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CLINICAL STUDY PROTOCOL
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TARCEVA (ERLOTINIB)**

An open-label multi-center study of erlotinib (Tarceva®) as first line therapy until and beyond RECIST progression in NSCLC patients who harbor EGFR mutations

PROTOCOL APPROVAL

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

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
b.i.d.	Twice Daily
BP	Blood pressure
CEA	Carcinoembryonic Antigen
CI	Confidence interval
C _{max}	Maximum plasma concentration
CR	Complete Response
CRF	Case Report Form[s]
CT	Computer Tomography
CNS	Central Nervous System
CXR	Chest X-Ray
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
ESF	eligibility screening form
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	intent to treat

iv	Intravenous
MRI	Magnetic Resonance Image
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-CTC	National Cancer Institute-Common Toxicity Criteria
NCI-CTCAE	National Cancer Institute-Common Toxicity Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease or Pharmacodynamic
PFS	Progression free survival
PS	Performance Status
PK	Pharmacokinetic
p.o.	Oral administration
PR	Pulse rate
PR	Partial Response
q.d.	Once daily administration
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
T _{1/2}	half-life
TNM	primary tumor/regional lymph nodes/distant metastasis
T _{MAX}	time to maximum plasma concentration
TTP	Time to Tumor Progression
ULN	Upper Limit of Normal

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PART I: STUDY DESIGN AND CONDUCT

1 BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Non Small Cell Lung Cancer

Lung cancer is both common and deadly. It is the second most common cancer in men as well as women, accounting for about 13% of cancer diagnoses, but it is the leading cause for cancer-related deaths in industrialized countries, killing more patients than breast, colorectal and prostate cancer together. It affected approximately 169,400 people in the United States of America (USA) in 2002 and about 80% of these were non-small cell lung cancer (NSCLC). The 5-year survival rate for all stages combined does not exceed 15%. Only 15% of all lung cancers are detected at an early operable stage [1,2]. Cigarette smoking remains the principal cause for lung cancer with 85 to 90% of all lung cancer patients having smoked cigarettes at some time.

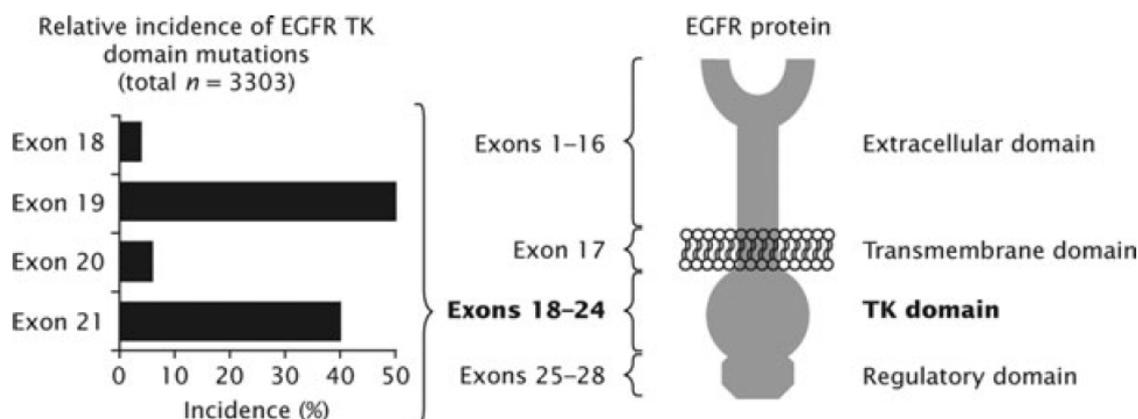
Platinum-based chemotherapy is the standard treatment for advanced NSCLC. It significantly improves survival and achieves better symptom control than best supportive care [3,4]. In phase III studies, combinations of cisplatin and taxanes, gemcitabine, vinorelbine and irinotecan have produced superior therapeutic results compared with cisplatin alone, but no particular two-drug, platinum-based combination has been identified as superior to the others [5-10]. A phase III study comparing four platinum-based doublets in patients with advanced NSCLC (cisplatin/paclitaxel, carboplatin/paclitaxel, cisplatin/docetaxel and cisplatin/gemcitabine) showed no significant advantage of one chemotherapy regimen over the others, with response rates between 17% and 22% and median survivals of approximately 8 months [10]. Three-drug chemotherapy combinations have increased toxicity but have not been proven more efficacious than two-drug combinations [11-16].

1.1.2 Molecular Biology of Epidermal Growth Factor Receptor (EGFR) Mutations

EGFR is a 170-kDa member of the ErbB or human epidermal receptor (HER) family of tyrosine kinase (TK) growth factor receptors. Mutations in the region of the EGFR gene that encodes the TK domain of the receptor were first reported in patients with NSCLC in 2004 [17,18]. Further molecular studies performed by a number of research groups have shown that EGFR mutations occur almost exclusively within exons 18-21 of the gene, which encodes the amino lobe and part of the carboxy lobe of the receptor (see Figure 1). Murray and colleagues have compiled an extensive database of published literature, containing data from over 12,000 patients, that has identified 254 independent somatic mutations in this region of the gene [19]. The most common mutations involve point mutations in exon 18, deletions and/or insertions in exon 19, insertions/duplications and point mutations in exon 20 and point mutations in exon 21. One mutation in exon 20 (T790M) appears to confer resistance to EGFR TKIs, although this is very rare among EGFR TKI-naïve patients [19]. Other mutations, occurring in the region of the EGFR gene encoding the TK domain, appear to confer sensitivity to EGFR TKIs. The best characterized of these are deletions in exon 19 around the ATP-binding cleft of the

receptor (particularly E746-A750del) and a missense mutation in exon 21 (L858R) (Figure 1).

Figure 1 Sites of common activating mutations in exons 18-21 of the epidermal growth factor receptor gene



Adapted from Paz-Ares et al. *J. Cell. Mol. Med.* Vol 14, No 1-2, 2010 pp. 51-69

1.2 Erlotinib (Tarceva®) Erlotinib is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase (EGFR-TKI). Erlotinib has been approved worldwide for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen. An overview of selected clinical information is presented here; Detailed nonclinical and clinical information are available in the erlotinib Investigator Brochure (IB).

1.2.1 Pharmacokinetics

The total clearance of erlotinib correlates with hepatic blood flow in dogs and rats given intravenous (IV) doses of 1 mg/kg. In contrast, the total clearance decreases and the plasma drug exposure increases supra-proportionately in rats and dogs given IV doses of >1 mg/kg. *In vitro*, erlotinib is oxidised slowly by liver microsomes. The majority of the absorbed dose is extensively metabolised in rats and dogs, and only a small amount is excreted as unchanged drug in urine, bile, and feces. The volume of distribution in rats and dogs is ~3 L/kg. The tumor-to-plasma concentration ratio in the murine/human tumor xenograft model ranges from 0.3:1 to 1:1. The terminal elimination half-life in rats and dogs is 1 to 2 hours. The oral bioavailability of an aqueous suspension is 77% in rats and ~88% in dogs. Plasma protein binding of erlotinib ranges from 92% to 95% in man, monkey, rat, and mouse and is 85% in the dog. Corrected for protein binding of 95%, at the average plasma concentration responsible for 50% inhibition of tumor growth (oral dose of 10 mg/kg/day in the murine/human tumor xenograft model), the unbound concentration of drug in the plasma is estimated to be 86 nM (34 ng/ml). The estimated unbound concentration of erlotinib in plasma is consistent (4-fold higher) with the I_{c50} for the *in vitro* cellular phosphotyrosine reduction assay and is 43-fold higher than the I_{c50} for the *in vitro* (isolated enzyme) tyrosine kinase assay. Finally, erlotinib plasma protein binding depends on the levels of α -1-acid glycoprotein (AAG). Thus, AAG might be a significant determinant of pharmacokinetic (PK) and possibly PK-pharmacodynamic relationships in patients.

The metabolism of erlotinib might be influenced by enzyme-inducing anti-epileptic drugs. In a recent study reported at the ASCO meeting in 2005, Cloughesy and colleagues reported different C_{min} level of erlotinib between patients taking enzyme-inducing anti-epileptic drugs (C_{min}=50 to 750mg/ml) and patients not taking enzyme-inducing anti-epileptic drugs (C_{min}=750 to 1500mg/ml) (Cloughesy *et al*, ASCO 2005).

More recently, Hamilton and colleagues reported the results of PKs in a subset of patients included in the BR.21 trial (erlotinib versus placebo in patients who previously failed after first-line chemotherapy). In their analysis, Hamilton and colleagues demonstrated a significantly lower concentration of erlotinib for patients with a current smoking history when compared with others.

Table 1 Results of PKs in a subset of patients included in the BR.21 trial

	All Erlotinib Treated N=485				PK Cohort N=133			
	Never (n=104)	Ex (n=263)	Current (n=71)	p-value	Never (n=39)	Ex (n=69)	Current (n=16)	p-value
% PR+CR	23.1	4.6	0	<0.0001	43.6	10.1	0	<0.0001
Median OS	12.3mo	5.5mo	6.1mo	<0.0001	17.0mo	13.3mo	10.5mo	0.030
Mean C _{min} Erlotinib					1448	1262	748	<0.0001

Patients with Hepatic Impairment. The influence of hepatic metastases and/or hepatic dysfunction on the pharmacokinetics of erlotinib is not yet known. However, erlotinib is eliminated by hepatic metabolism and biliary excretion. Although erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7-9) compared with patients with adequate hepatic function, caution should be used when administering erlotinib to patients with hepatic impairment. Dose reduction or interruption of erlotinib should be considered if severe adverse reaction occurs.

Patients with Renal Impairment. No clinical studies have been conducted in patients with compromised renal function since erlotinib and its metabolites are not significantly excreted by the kidneys.

Drug–Drug Interactions. Co-administration of erlotinib with an inhibitor of CYP3A4 metabolism (ketoconazole, 200mg po BID for 5 days) resulted in increased exposure to erlotinib (an 86% increase in median erlotinib exposure [AUC]) and a 69% increase in peak plasma concentration (C_{max}), compared with administration of erlotinib alone. A dose reduction may be necessary when erlotinib is co-administered with potent CYP3A4 inhibitors.

Induction of CYP3A4 metabolism by a known enzyme inducer (rifampin, 600 mg po QD for 7 days) resulted in a 69% decrease in the median erlotinib AUC, compared with

administration of erlotinib alone. However, the effect of rifampin on C_{max} was negligible. Therefore, when erlotinib is co-administered with potent CYP3A4 inducers, erlotinib levels may drop significantly.

International normalized ratio (INR) elevations and/or bleeding events have been reported in some cancer patients taking warfarin while on erlotinib. Patients taking warfarin or other warfarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

A list of CYP3A4 inhibitors and inductors is provided in Appendix 5.

More detailed information on the pharmacokinetics of erlotinib can be found in the latest version of the erlotinib IB.

1.2.2 Erlotinib as 2nd/3rd line therapy in advanced NSCLC

The pivotal study BR.21, is a multinational randomized double-blind Phase III study, conducted by the NCIC [20]. Patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen were randomized 2:1 to receive either 150 mg erlotinib or placebo daily. A total of 731 patients were entered. All study endpoints were met, a statistically significant improvement over survival was observed with mOS of 6.67 mos in erlotinib and 4.70 mos in placebo ($p=0.002$). For the 727 patients evaluable for safety (485 erlotinib, 242 placebo), the majority of adverse events seen in the erlotinib arm were rash (75% erlotinib, 17% placebo) and diarrhoea (54% Erlotinib, 18% placebo) events. The majority of these events were mild to moderate in severity. More details can be found in the IB.

1.2.3 Erlotinib as 1st line therapy in advanced NSCLC

The early attempt of concomitant use of erlotinib with double chemotherapy as first line therapy was unsuccessful with two negative phase III trials (TALENT and TRIBUTE). Based on the hypothesis of potential pharmacodynamic interaction, an alternative approach was proposed by Mok and his colleagues, erlotinib was intercalated with platinum-double chemotherapy. Encouraging results were reported from a phase II randomized controlled trial [21], this approach is currently under phase III investigation.

1.2.3.1 First line maintenance therapy

Recently, Cappuzzo and his colleagues have reported a positive double-blind placebo-controlled phase III trial (SATURN; BO18192) [22]), which investigated erlotinib monotherapy in patients with advanced NSCLC who had non-progressive disease following first-line platinum-doublet chemotherapy. The maintenance therapy with erlotinib for patients in this trial is well tolerated and significantly prolongs PFS compared with placebo. First-line maintenance with erlotinib could be considered in patients who do not progress after four cycles of chemotherapy.

884 patients were analysable for PFS; 437 in the erlotinib group and 447 in the placebo group. After a median follow-up of 11.4 months for the erlotinib group and 11.5 months for the placebo group, median PFS was significantly longer with erlotinib than with placebo: 12.3 weeks for patients in the erlotinib group versus 11.1 weeks for those in the placebo group (HR 0.71, 95% CI 0.62-0.82, $p<0.0001$). PFS was also significantly longer

in patients with EGFR-positive immunohistochemistry who were treated with erlotinib (n=307) compared with EGFR-positive patients given placebo (n=311, median PFS 12.3 weeks in the erlotinib group vs 11.1 weeks in the placebo group, HR 0.69, 95% CI 0.58-0.82, p<0.0001). The most common grade 3 or higher adverse events were rash (37 [9%] of 443 patients in the erlotinib group vs none of 445 in the placebo group) and diarrhoea (seven [2%] of 443 patients vs none of 445). Serious adverse events were reported in 47 patients (11%) on erlotinib compared with 34 patients (8%) on placebo. The most common serious adverse event was pneumonia (seven cases [2%] with erlotinib and four [$<1\%$] with placebo).

A total of 889 patients were included in this study. A pre-planned subgroup analysis of EGFR mutation patients was performed, as it has been strongly suggested that EGFR mutations may be a strong predictive biomarker for PFS in patients receiving erlotinib. Erlotinib significantly improved PFS when patients were treated with erlotinib maintenance therapy compared with placebo (HR=0.09, p<0.0001). Regarding safety, no mutated patient receiving erlotinib in this trial experience a serious adverse event or discontinued the treatment due to an adverse event.

1.2.3.2 First line therapy in EGFR Mutations

EGFR mutations and EGFR TKIs

Molecular studies from patients responding to tyrosine kinase inhibitors (TKIs) have demonstrated that certain mutations in the exons 19 and 21 of the *EGFR* gene occur more frequently in patients who responded to the therapy. It has been observed that 70-90% of patients with some of these alteration (EGFR exon 19 deletion and EGFR exon 21 L858R respond to TKIs [23-25]. These data suggested that the presence of mutations can be used to identify a subgroup of patients with NSCLC in whom this growth factor plays a critical role in tumor growth and in which the inhibition with TKIs would be more effective and safe compared to platinum based chemotherapy.

The following two randomized studies performed in an Asian population suggest that EGFR TKIs should be indicated in the first line treatment of NSCLC patients with EGFR mutations rather than platinum-based doublet chemotherapy.

Mok et al. presented the IPASS study at the ESMO congress in 2008[26]. This was a first line study of gefitinib vs carboplatin/paclitaxel in non or light ex-smoking Asian patients with advanced adeno NSCLC. The primary end point of this study was PFS.

Prof Fukuoka presented the results related to patients with EGFR mutated tumours included in this study. Out of the 1217 patients included, 437 were available for mutation analysis and out of those 261 (60%) presented with an EGFR mutation. The study demonstrated that mutated patients treated with gefitinib presented higher ORR (71.2% vs 47.3%) and PFS (9.5 months vs 6.3 months) than those patients treated with chemotherapy (p <0.0001 for both parameters) [27].

At the same meeting another phase III study was presented comparing gefitinib versus Paclitaxel/carboplatin chemotherapy in patients with EGFR mutations by Dr Kobayashi [28]. This trial, performed in Japan, included 198 patients (98 vs 100 patients in gefitinib vs chemotherapy, respectively). PFS was the primary end-point. Both ORR and PFS were

superior for the gefitinib arm (74.5% vs 29% and 10.5 months vs 5.5 months for gefitinib vs chemotherapy, respectively).

Erlotinib in EGFR mutations

There is a body of clinical evidence that suggests patients with advanced NSCLC whose disease is EGFR mutation positive respond better to treatment with TKIs compared to platinum based chemotherapy.

The Spanish Lung Cancer Group have presented a prospective phase II trial in patients with advanced NSCLC bearing mutations in the TK domain [29]. Patients presenting with mutations (exon 19 deletions or L858R mutation in exon 21) were eligible to receive erlotinib 150 mg as first line treatment until PD or toxicity.

Out of all screened patients 43 were included in the trial, 38 were evaluable for response. As a total, 31 (82%) patients presented an objective response (95% and 67% for exon 19 and 21, respectively). With a median follow-up of 7 months, the median TTP was 13.3 months and the Survival at 1 year was 82%.

The safety profile of patients with EGFR mutated tumors did not present any new significant findings in this western population study as it was shown by SLCG [29] presented at ASCO 2006. As already reported with TKIs, rash and diarrhoea were the most common toxicity but were usually mild with only few patients presenting grade 3. No grade 4 adverse events were reported in this trial. It is also worth highlighting that no patient presented Interstitial Lung Disease (ILD) in this western population.

The Spanish Lung Cancer Group (SLCG) presented additional prospective analyses to support these findings at ASCO 2009 [30]. This analysis included 358 patients with mutations of the EGFR gene in the 1st and 2nd line setting. The results were outstanding, with 71% of ORR, median TTP of 14 months and median OS of 27 months.

Most recently a phase III randomized controlled trials (OPTIMAL) was reported at ESMO 2010 in Chinese advanced NSCLC patients whose tumors have activating EGFR mutations received erlotinib versus chemotherapy. Details are reviewed in Section 3.1.3.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the efficacy measured by progression free survival by RECIST 1.1 (PFS1) of erlotinib monotherapy as first line therapy in stage IV or recurrent NSCLC patients with EGFR mutated tumors.

2.2 Secondary Objectives

- Progression free survival by investigator's discretion (PFS2*) in all patients and a subset of patients with E19del or L858R mutation

(*defined as the length of time from first study dose until Off-erlotinib PD; the Off-erlotinib PD is assessed based on investigator's discretion of overall clinical evaluation not limited to RECIST criteria.)

- Objective response rate (CR + PR) in all patients and patients with EGFR mutated tumors (E19del or L858R)
- Disease control rate (CR + PR + SD) in all patients and patients with EGFR mutated tumors (E19del or L858R)
- Progression free survival (PFS) in patients with EGFR mutated tumors (E19del or L858R)
- Overall survival (OS) in all patients and patients with EGFR mutated tumors (E19del or L858R)
- Safety profile using NCI CTC AE (version 4.0)
- Assess the correlation between EGFR mutations in plasma with clinical outcome

2.3 Exploratory Objectives

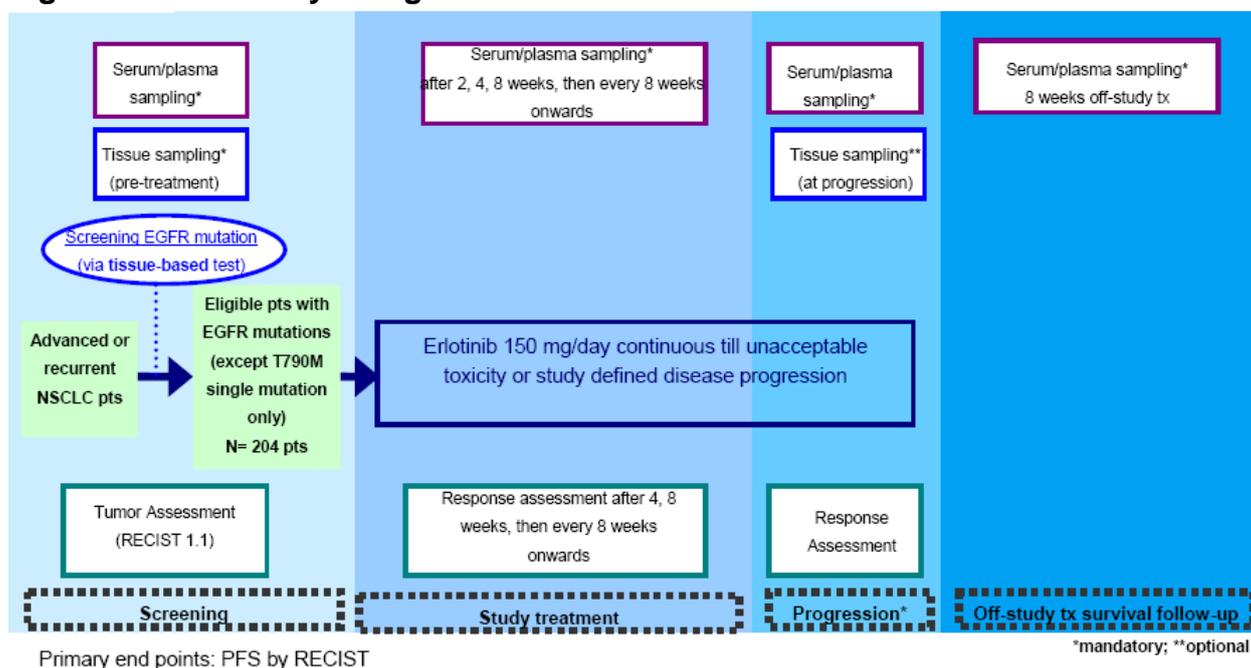
Roche is committed to the collection of biomarker samples in all clinical study protocols. The objective of biomarker profiling is to enable development of treatments specifically targeted for optimal patient benefit (personalized healthcare). Biomarker samples will be stored in the Roche Clinical Repository (RCR). The (RCR) is a centrally administered facility for the long term storage of human biological specimens including body fluids, solid tissues and derivatives thereof (e.g. DNA, RNA proteins/ peptides). Specimens stored in the RCR will be used to:

- Study the association of biomarkers with efficacy and/ or adverse events associated with medicinal products; and/ or
- Increase our knowledge and understanding of disease biology; and/or
- Develop biomarker or diagnostic assays; establish the performance characteristics of these assays.

3 STUDY DESIGN

This is a large multi-center single arm open-label Phase II study.

Figure 2 Study Design Schema



Notes:

1. Disease progression (PD) is defined by: either RECIST PD or Off-erlotinib PD (only for those patients who continue erlotinib after RECIST PD). If patients continue erlotinib after RECIST PD upon investigator's discretion, an additional tumor assessment is recommended 4 weeks post RECIST PD.
2. Screening EGFR mutation test (tissue-based) must be performed at one of study designated local laboratories to ensure consistent quality.
3. Tissue, serum and plasma samples will be collected for all screening patients. Tissue samples will be used for mutation test at local lab, the remaining samples will be collected and shipped to central laboratory along with serum/plasma samples for central biomarker analysis.

3.1 Overview of Study Design

3.1.1 Biomarker study

The biomarker study consists of

- Mandatory consent to participate tumor tissue sample collection **at screening** and biomarker analysis - FFPE histology specimen, block or 10-20 slides; and mandatory consent to participate serum/plasma sampling **at screening** and biomarker analysis (see details in Tables 2 & 3).
- Mandatory consent to participate serial serum/plasma sampling **during the study till 8 weeks off study treatment** and biomarker analysis IF a patient is deemed **eligible** for the study (see details in Table 3).
- Optional consent to re-biopsy and tumor tissue sample collection **at the time of disease progression** and biomarker analysis IF a patient has biopsy accessible tumor and no contraindications - FFPE block or 5-15 slides (see details in Table 2).

3.1.2 Erlotinib beyond RECIST progression

In general, erlotinib beyond RECIST progression in all patients is not recommended. However, under circumstances dosing beyond RECIST progression should be considered when it is felt that the patient may clinically benefit by continued therapy as judged by

the investigator. (*note: below only provides examples and not limited to. In all cases, investigator's discretion shall apply*)

Patients may be considered to continue erlotinib upon first RECIST PD, for example:

- Slow progression with more than 6 months of disease control duration (PR or SD)
- Asymptomatic minimal progression
- Mixed responses
- New brain metastasis which can be adequately controlled by local therapy
- Malignant pleural effusion which can be controlled by pleurodesis
- Scanty sites of bone metastasis progression

Patients shall be considered to be taken off erlotinib at first RECIST progression, for example:

- Definitive extracranial progression with symptoms
- Rapid progression and/or worsening of performance status
- Life-threatening complications

The decision of continuation or dis-continuation of erlotinib will be based on investigator's discretion of overall clinical evaluation **NOT** limited by RECIST criteria. However, tumor assessment will be continued according to defined schedule as long as the patient is on erlotinib treatment.

At the investigator's discretion, patients who have the initial RECIST PD may continue erlotinib. At any time, if assessed by the investigator that the patient is no longer benefit from erlotinib, then the patient shall come off study medication. Local therapy such as radiotherapy or radiofrequency ablation etc. is acceptable during the study. Due to limited evidence, caution must apply for concurrent use of erlotinib with other treatment modalities, close safety monitoring is mandatory if applicable.

3.1.3 Rationale for Study Design

Erlotinib monotherapy in EGFR mutated NSCLC as first line therapy has demonstrated promising efficacy with reported PFS ranging from 13-15 months [31,32,33]. Most recently, Zhou and his colleagues reported a randomized phase III trial (CTONG 0802 trial) investigated erlotinib versus chemotherapy as first line therapy in Chinese patients with activating EGFR mutations at ESMO 2010 [33]. Based on the intent-to-treat analysis, erlotinib provided an almost 3-fold increase in PFS versus chemotherapy (13.1 vs 4.6 months, HR 0.16, 95% CI 0.10-0.26, $p < .0001$). Among secondary endpoints, erlotinib provided significantly improved objective response rate (83% vs 36%, $p < .0001$) and disease control rate (96% vs 82%, $p = .002$). Overall survival data are not yet available. PFS benefits were consistent across all of the subgroup analyses, including age, gender, ECOG PS, smoker status and histology. Another phase III randomized trial by SLCG (EURACT trial) conducted in Europe is currently ongoing.

Riely and colleagues have reported that patient may continue to derive benefit from erlotinib after disease progression, discontinuation of EGFR TKI leads to more rapid progression of disease (symptoms, tumor size, and FDG-avidity on PET scan) [34]. This strategy mirrors the experience in other oncogene-addicted cancers, particularly HER2-amplified breast cancer. In women with HER2-amplified breast cancer who have had progression of disease on trastuzumab, improved radiographic response rate, time to progression, and overall survival are observed when conventional chemotherapy is added to trastuzumab [35].

The purpose of our trial is to further investigate the efficacy and safety of erlotinib in EGFR mutated NSCLC prospectively in a large single arm cohort. In addition, tumor tissue (pre-treatment and at progression) and serum/plasma (pre- and during the treatment, at the time of progression and off treatment) will be collected and analyzed retrospectively, for markers correlate with sensitivity and resistance as well as the potential of monitoring the treatment effect, all of which will provide further understanding of erlotinib as first line therapy in EGFR mutated NSCLC. In this study, patients are allowed to continue erlotinib beyond RECIST progression upon investigator's discretion, this part is exploratory for potential identification of patients characteristics and biomarker profile in correlation with further clinical benefit. Furthermore, serum marker carcinoembryonic antigen (CEA) will be explored for potential correlation with clinical outcome [36].

3.1.4 Rationale for Dose Selection

The selection of the 150 mg/day dose of erlotinib for this single-agent study was based on pharmacokinetic parameters, as well as the safety and tolerability profile of this dose observed in Phase I, II and III trials in heavily pre-treated patients with advanced cancer. Drug levels seen in the plasma of patients with cancer receiving the 150 mg/day dose were consistently above the average plasma concentration of 500 ng/mL targeted for clinical efficacy.

3.1.5 End of Study

The study will end 42 months after the first patient is recruited. For all patients who have discontinued study drug treatment and are alive, information on survival will be collected.

3.2 Number of Subjects

Approximately 204 patients whose tumor has EGFR mutation(s) in exon 18 through to exon 21 (except T790M single mutation alone) will be recruited over a planned recruitment period of 14 months.

3.3 Centers

Approximately 23 centers will participate in this study.

4 STUDY POPULATION

Under no circumstances are subjects who enrol in this study permitted to be enrolled for a second course of treatment.

4.1 Inclusion Criteria

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

1. Male or female patients aged ≥ 18 years.
2. Patients able and willing to give written informed consent. Consent must be obtained prior to any study-specific procedure.
3. Histologically or cytologically confirmed stage IV or recurrent NSCLC.
4. Patients give written consent to participate biomarker sampling and analysis.
[note: histology samples are required for screening tissue sampling]
5. Presence of mutation(s) in exon 18 through to exon 21 of EGFR-receptor (except T790M single mutation only).
6. Measurable disease, i.e. at least one lesion, not previously irradiated, as ≥ 10 mm in the longest diameter (≥ 15 mm in short axis for lymph node).
7. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
8. Life expectancy of at least 3 months.
9. Adequate hematological function: Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, and Platelet count $\geq 100 \times 10^9/L$, and Hemoglobin ≥ 9 g/dL
10. Adequate liver function: Total bilirubin $< 1.5 \times$ upper limit of normal (ULN), and aspartate aminotransferase (AST), alanine aminotransferase (ALT) $< 2.5 \times$ ULN in patients without liver metastases; $< 5 \times$ ULN in patients with liver metastases.
11. Adequate renal function: Serum creatinine $\leq 1.5 \times$ ULN and creatinine clearance ≥ 45 ml/min.
12. International normalized ratio (INR) ≤ 1.5 and activated prothrombin time (aPTT) $\leq 1.5 \times$ ULN within 7 days prior to first study dose.
13. Patients assessed by the investigator to be able to comply with the required protocol and follow-up procedures, and able to receive oral medications.

4.2 Exclusion Criteria

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

1. Patients with T790M single mutation alone.
2. Patients with prior exposure to agents directed at the HER axis (e.g. erlotinib, gefitinib, cetuximab, trastuzumab).
3. Patients with prior chemotherapy or systemic anti-cancer therapy (e.g. monoclonal antibody therapy) for advanced NSCLC disease.
 - Previous adjuvant or neo-adjuvant treatment for non-metastatic disease is permitted if completed ≥ 6 months before the start of study treatment.
 - Prior surgery is permitted if performed ≥ 4 weeks before the start of study treatment and the patient is fully recovered.
 - Prior localized radiotherapy is permitted if it was not administered to the only target lesion and provided radiotherapy has been completed ≥ 2 weeks before the start of study treatment and the patient is recovered from toxicity
 - Symptomatic or uncontrolled central nervous system (CNS) metastases are excluded. Patients with asymptomatic brain metastases are allowed and must be clinically stable and off steroid for at least 2 weeks prior to the start of study treatment.
4. Treatment with an investigational drug agent during the 3 weeks before enrollment in the study.

5. Other malignancy within the last 5 years, except for carcinoma in situ of the cervix or basal cell carcinoma or squamous cell skin cancer, or localized prostate cancer treated surgically with curative intent, DCIS treated surgically with curative intent.
6. Known hypersensitivity to erlotinib or any of its excipients.
7. 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.
8. Patients with pre-existing parenchymal lung disease such as pulmonary fibrosis.
9. Coumarins (CoumadinTM; warfarin) use. If the patient requires anti-coagulation therapy, the use of low molecular weight heparin instead of coumarins is recommended where clinically possible.
10. Incapacity to take oral medication or previous surgical procedures that affect absorption and imply the need for intravenous or parenteral feeding.
11. Severe uncontrolled systemic disease (e.g. hypertension, clinically significant cardiovascular, pulmonary, metabolic, wound-healing, ulcer, or bone fracture).
12. Active HBV, active HCV or known HIV infection.
13. Pregnant or lactating women.
14. Woman of childbearing potential with either a positive or no pregnancy test at baseline. Postmenopausal women must have been amenorrhoeic for at least 24 months to be considered of non-childbearing potential.
15. Patients (male or female) of reproductive potential not willing to use effective method of contraception during the study and for a period of 90 days following the last administration of erlotinib.

[note: 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.]

4.3 Concomitant Medication and Treatment

At study initiation, patients should continue with their concomitant medications, as directed by their physician.

All concomitant medication must be recorded on the CRF. Additionally, any diagnostic, therapeutic or surgical procedure performed during the study period, should be recorded including the date, indication, description of the procedure(s) and any clinical findings.

No other experimental, active or passive immunotherapy or systemic anticancer therapy is permitted except for localised radiotherapy (providing that it doesn't compromise tumor assessments [non target tumor]) for pain control. It is strongly recommended that Chinese herbal medicine should not be administered because the ingredients of many complementary herbal medicines are not fully studied.

4.3.1 Concomitant Medications and Therapies Requiring Special Attention

- Caution should be exercised when erlotinib is co-administered with CYP3A4 inhibitors and inducers (see section 7.2.1). As grapefruit juice has the potential to inhibit CYP3A4 activity, it is recommended that patients do not drink grapefruit juice

- during the study.
- Coumarins (e.g. warfarin) are strongly discouraged during erlotinib therapy. If the patient requires anti-coagulation therapy, then the use of low molecular weight heparin instead of coumarins is recommended where clinically possible. If inevitable, frequent monitoring of INR and prothrombin time must be performed.
 - Patients with dry eyes (an abnormal Schirmer's test results on baseline ophthalmologic exam) should be advised to use an ocular lubricant.
 - Patients who continue to wear contact lenses may have an increased risk of ocular adverse events. The decision to continue to wear contact lenses should be discussed with the investigators and ophthalmologist.
 - The exposure to erlotinib and its metabolites was significantly decreased when erlotinib was co-administered with the proton pump inhibitor omeprazole (Study BP20046, Roche data on file). Therefore proton pump inhibitors should be avoided while on study. If necessary, alternatives should be considered.
 - Concomitant bisphosphonate use to control pain is permitted.
 - Appropriate anti-emetic medication should be given.
 - Any medication contraindicated when using erlotinib is not permitted and special warnings and precautions for using erlotinib should be observed.

4.4 Criteria for Premature Withdrawal

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

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

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

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

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of subjects should be avoided. Should a subject decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

4.4.1 Withdrawal Of Subjects From the Roche Clinical Repository (RCR)

RCR specimens may be withdrawn from the RCR at any time for any reason. If a subject wishes to withdraw his/her consent to the testing of his/her specimen(s), the investigator must inform the Roche monitor in writing of the subject's wishes using the withdrawal form provided and enter the date of withdrawal in the subject's Case Report Form (CRF). A subject withdrawal from the main trial does not, by itself, constitute withdrawal of the specimen from the RCR likewise, a subject withdrawal from the RCR does not constitute a withdrawal from the main trial.

4.5 Replacement Policy (Ensuring Adequate Numbers of Evaluable Subjects)

4.5.1 For Subjects

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

4.5.2 For Centers

A center may be replaced for the following administrative reasons:

- Excessively slow recruitment.
- Poor protocol adherence.



5 SCHEDULE OF ASSESSMENTS AND PROCEDURES

Table 2 Schedule of Assessments

Assessment	Screening		Eligible patients with EGFR mutation(s) (except T790M single mutation only) ⁱ	Baseline	Study Treatment Phase (+/- 3 days)	Disease Progression ^k / Study tx completion	Survival Follow-up Phase (+/- 1 week)
	Study Day			Study Day	Visit 1 onwards		Visit 1 onwards
	-21	-7		1	Day 1 of weeks 3, 5 and 9, then every 8 weeks onwards		Every 8 weeks
Informed consent	X						
Demographics, medical history	X						
Pregnancy test ^a		X			<i>To be repeated as clinically indicated^l</i>		
Chest x-ray	X				<i>Day 1 of week 3 then to be repeated as clinically indicated^l</i>		
Physical examination ^b		X			X		
Weight, Height ^m		X		X	X		
Vital signs		X		X	X		
ECOG PS		X		X	X		
ECG	X				<i>To be repeated as clinically indicated^l</i>		
Mandatory tumor sampling ^j	X					X (optional)	
Mandatory blood sampling (serum/plasma)	X					Refer to Table 3 for serum and plasma sampling schedule	
Hematology ^{c, d}		X			X		
Biochemistry ^e		X			X		
Carcinoembryonic antigen (CEA)		X			<i>Day 1 of weeks 3, 5 and 9</i>		
Urinalysis		X			<i>To be repeated as clinically indicated^l</i>		
Concomitant medications	X	X				Record throughout study tx phases and for 28 days after last study dose	
Tumor assessment	X ^f					Weeks 4, 8, then every 8 weeks onwards until disease progression^k	
Adverse events ^g	X	X				Record throughout study tx phases and for 28 days after last study dose	
Subsequent therapy for NSCLC ^h							X
Erlotinib dispensing				X	X		



Table 3 Schedule of Serum and Plasma Sample Collection

	Screening (- 21 days, pre-treatment)	<u>Day 1</u> of week 3, week 5, week 9, then every 8 weeks onwards (+/- 3 days)	RECIST PD	Off-erlotinib PD (<u>ONLY</u> for patients continued erlotinib after RECIST PD)	<u>Day 1</u> of week 9 off-erlotinib (+/- 1 week)
Blood draw for plasma isolation	20 ml	5 ml at each time point	15 ml	15 ml	15 ml
Blood draw for serum isolation	5 ml	5 ml at each time point	5 ml	5 ml	5 ml

Table 2 Notes

- a. Urine or serum pregnancy test within 3 days of first study dose in women of childbearing potential.
- b. Including an ophthalmologic examination if clinically indicated.
- c. Hematology: leukocytes with neutrophils, hemoglobin, and platelets.
- d. Hematology: INR or aPTT at screening only, then to be repeated if clinically indicated or if patient receives anti-coagulants during the study treatment.
- e. Biochemistry: alkaline phosphatase, ASAT, ALAT, bilirubin, serum creatinine, potassium and sodium.
- f. Tumor assessment consists at minimum of CT/MRI scans of chest, upper abdomen (incl. liver and adrenal glands) and brain at the screening. 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. Post-baseline tumor assessments are to be performed within +/- 1 week for scheduled visits during the study treatment phase. 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. CT/MRI tumor scans performed as routine practice and prior to study consent can be used as baseline if comply with study requirement. A negative brain CT/MRI scan result 8 weeks prior to the study start is acceptable, however if there is clinical suspicion of brain lesion, a brain scan must be performed within 21 days.
- g. Graded according to NCI CTC-AE version 4.0.
- h. Subsequent second line and third line treatment information with corresponding best overall responses and progression free survival, for choice of second line therapy, a standard platinum-doublet chemo regimen would be recommended for suitable patients upon investigator's discretion.
- i. EGFR mutation test performed at study designated local labs but prior to study consent is acceptable if the test and results comply with study requirement and patients have adequate tissue sample to participate mandatory sampling.
- j. At the study entry, biomarker tissue sampling consent for screening is mandatory and at the time of disease progression is optional. Patients must have either an archival or fresh-biopsy pre-treatment histology sample to be eligible for the study.
- k. Disease progression (PD) is defined by: either RECIST PD or Off-erlotinib PD (only for those patients who continue erlotinib after RECIST PD). If patients continue erlotinib after RECIST PD upon investigator's discretion, an additional tumor response assessment is recommended 4 weeks post RECIST PD.
- l. Any abnormality or changes from baseline which is clinically significant and/or requires intervention, shall be reported as adverse event.
- m. Height only required at screening.

5.1 Screening Examination and Eligibility Screening Form

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

A screening examination should be performed within 21 days time window before first study dose, patients who fulfill all the inclusion and none of the exclusion criteria will be accepted into the study.

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

A screen failure log must be maintained by the investigator.

5.2 Procedures for Enrollment of Eligible Subjects

The investigator or designee will use the Case Report Form pre-printed with the assigned subject number and in the appropriate place on each subject's CRF.

5.3 Clinical Assessments and Procedures

5.3.1 Tumor Response Criteria

Tumor response will be evaluated according to the RECIST criteria (version 1.1, see appendix 2).

In this study, tumor response will be measured using CT and/or MRI. For each subject, the same method of assessment and the same technique **must** be used to evaluate each lesion throughout the entire study. If more than one method is used, select the most accurate method according to RECIST when recording data.

Consistency of consecutive CT-scans or MRIs should be ensured during all assessments for each patient, with the same technique being used for evaluating lesions throughout the treatment period. **(Use of spiral CT or MRI is required for baseline lesions <20 mm and used consistently throughout the study.)** The use of oral and IV contrast etc. should, as long as it is clinically possible, be kept consistent. Tumor measurements should be made by the same investigator/radiologist for each patient during the study to the extent that this is feasible. In case of clinically measurable superficial (such as skin) lesions, repeated photographs should be used to document tumor response. These photos must include a ruler for documentation purposes.

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

Scheduling of tumor assessments

Baseline total tumor burden must be assessed within a maximum of 3 weeks before first dose of study drug treatment. Post-baseline assessments are to be performed at weeks 4, 8 then every 8 weeks onwards. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment

should be performed. If patients continued erlotinib after first RECIST PD upon investigator's discretion, an additional tumor assessment 4 weeks post first RECIST PD is recommended.

CT/MRI tumor scans performed as routine practice and prior to study consent can be used as baseline if comply with study requirement. A negative brain CT/MRI scan result 8 weeks prior to the study start is acceptable, however a brain scan must be performed within 21 days if there is clinical suspicion of brain lesion.

All tumor assessments after baseline will be done within 7 days of the scheduled visit. If a subject inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the subject may continue treatment until the next scheduled assessment, unless signs of clinical progression are present.

5.3.2 Performance status

Performance Status (PS) will be measured using the ECOG Performance Status Scale (see appendix 3). It is recommended, where possible, that a subject's PS will be assessed by the same person throughout the study. PS will be assessed at each visit.

5.3.3 Clinical Safety Assessments

The NCI CTC-AE **version 4.0** will be used to evaluate the clinical safety of the treatment in this study. Subjects will be assessed for adverse events at each clinical visit and as necessary throughout the study. A complete medical history (including demographics, NSCLC history, smoking history, cancer/treatment, co-morbidities) will be performed at screening. A physical examination* and ECG will be performed at screening then as indicated. Chest X-ray will be performed at screening, day 1 of week 3 then as indicated.

* If clinically indicated, an ophthalmologic exam may be performed as needed.

5.3.4 Laboratory Safety Assessments

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

The following laboratory parameters will be assessed for patient safety:

Hematology: leukocytes with neutrophils, hemoglobin, and platelets

Coagulation tests: INR, aPTT. (at screening only, then to be repeated if clinically indicated or if patient receives anti-coagulants during the study treatment)

Blood chemistry: AST, ALT, total bilirubin, ALP, serum creatinine, K+, Na+

Pregnancy Test: Urine or serum within 3 days of first study drug dose.

Urinalysis (at screening only, to be repeat only clinically indicated)

The time points for these tests are defined in the schedule of assessments. Additional tests may be performed at the discretion of the investigator.

Local laboratories will be used for all laboratory tests, with test results for the laboratory test recorded in the laboratory results section of the CRF.

Creatinine clearance is required only at screening. Results based on 24 hour urine collection are acceptable in patients where Cockcroft-Gault formula is considered inadequate.

5.3.5 Molecular Assessments

Tissue sampling and analysis

Pre-treatment tissue samples (histology) from archival tumors or diagnostic tissue biopsy will be collected for **all screening patients**. Formalin fixed paraffin embedded (FFPE) tumor **tissue blocks or 10-20 slides** will be collected. These tissues may be from the primary tumor, or a metastatic site (or site of local recurrence or advancement) if the primary tumor is unavailable, or if possible from both primary tumor and a metastatic site. Samples shall be sent to Roche designated local laboratory for:

- 1). EGFR mutation test for eligibility screening, EGFR mutation test results shall be recorded on CRF;
- 2). The remaining tissue samples after EGFR mutation test, will be sent to central lab for biomarker analysis, markers of angiogenesis, markers of tumor biology, tumor necrosis, vascularity, cell turnover, and expression of molecules in gene HER families and their signaling pathway molecules may be assessed.

At disease progression, fresh tissue biopsy for sample collection and analysis is optional.

Serum/plasma sampling and analysis

Pretreatment and post-treatment plasma and serum samples will be obtained at various time points as shown in Table 3. Samples will be initially stored at the site in -70°C freezer before shipping to the central lab. These samples will be used for biomarker assays which may include EGFR mutations and other candidate NSCLC biomarkers.

Serum marker for carcinoembryonic antigen (CEA)

Pre-treatment and post-treatment (day 1 of weeks 3, 5 and 9) serum tumor marker (CEA) will be measured at local lab, for explore the correlation of tumor marker responses and radiographic responses [36].

5.4 Roche Clinical Repository (RCR) Specimen(s)

Specimens for dynamic (non inherited) biomarker discovery and validation will be collected from all patients consent to the trial.

These specimens will be used for research purposes to identify biomarkers that are predictive of response to erlotinib treatment (in terms of dose, safety and tolerability) and will help to better understand the pathogenesis, course and outcome of NSCLC and related diseases. To these ends analysis may include determination of markers of HER family, their signaling pathway molecules and other cancer related markers.

The results of specimen analysis from the RCR will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for subjects in the future.

All RCR specimens will be destroyed no later than 15 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period. The specimens in the RCR will also be made available for future biomarker research towards further understanding of erlotinib treatment of NSCLC, related diseases and adverse events and for the development of potential associated diagnostic assays. The implementation and use of the RCR specimens is governed by the Roche Clinical Repository policy to ensure the appropriate use of the RCR specimens. If no consent has been given for long term storage, all samples will be destroyed no later than 5 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period.

5.4.1 Specimen Types for Screening and Central Biomarker Analysis

For sampling procedures, storage conditions and shipment instructions, see study Sample Handling and Logistics Manual.

Tumor FFPE histological specimen

Screening:

One entire tumor block or 10-20 slides with proven histopathology will be needed for biomarker analysis. The block can first be used for local routine diagnosis. It is extremely important that the provided tissue contains sufficient tumor cells (>100 / section) in order to perform the planned analyses. The tumor block has to be preserved in formalin/formaldehyde, other fixatives may lead to failure of the analyses. 1 year after completion of the study, the tumor blocks will be returned to the sites upon request, remaining slides will not be returned but destroyed.

At disease progression:

One entire tumor block or 5-15 slides with proven histopathology will be needed for biomarker analysis. See above for other details.

Only acceptable if patient also has histology specimen - Tumor cytological specimen

One entire block or approximately 10 slides with proven histopathology will be needed for analysis. The block can first be used for local routine diagnosis. It is extremely important that the provided specimen contains sufficient tumor cells (>50 / section) in order to perform the planned analyses. Remaining slides will not be returned but destroyed.

Assay Descriptions

Adequate technologies and protocols will be used to evaluate molecular markers (e.g. but not limited to immunohistochemistry, *in-situ* hybridization, quantitative polymerase chain reaction, direct sequencing or enzyme-linked immunosorbent assay)

Plasma / Serum assays

Blood for plasma and serum isolation will be obtained at various time points as shown in Table 3.

For all samples, dates of consent and specimen collection should be recorded on the case report form (CRF).

6 INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Dose and Schedule of IMP

Erlotinib 150 mg/day oral daily until disease progression or unacceptable toxicity.

6.2 Preparation and Administration of IMP and Comparator(s)

Tarceva® tablets will be provided in blisters. In addition to the active ingredient erlotinib, the tablets contain lactose monohydrate, cellulose, sodium starch glycolate, sodium laurel sulfate, and magnesium stearate. The tablets are film-coated white to yellowish, round, biconvex with print coloration according to tablet strength.

Study medication will be provided in blister packs containing either 25 mg, 100 mg, or 150 mg erlotinib. All dose levels will be supplied as 30-day blister packs. Study medication will be labeled in accordance with ICH Good Manufacturing Practice.

Tablets remain stable in their packs for 3 years. There are no special requirements for storage but room temperature is optimal.

Tablets should be taken preferably in the morning with up to 200 mL of water. On the visit days, study drug will be taken in the clinic as instructed by the study nurse or the investigator. Erlotinib tablets should be taken 1 hour before or 2 hours after meals. Patients who are unable to swallow the tablets may dissolve the tablets in the distilled water for administration.

In case of emesis after taking erlotinib, the patient should NOT take another tablet.

6.3 Formulation, Packaging and Labeling

Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the study medication will be in accordance with Roche standards and local regulations. The study drug must be stored according to the details on the product label. The drug label indicates the storage temperature.

The drug label indicates the storage temperature. Local packaging in some countries may be different.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

6.4 Blinding and Unblinding

Not applicable, study is open-label.

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.

Accurate records must be kept for each study drug provided by the sponsor. These records must contain the following information:

- Documentation of drug shipments received from the sponsor (date received and quantity)
- Disposition of unused study drug not dispensed to patient

A Drug Dispensing Log must be kept current and should contain the following information:

- the identification of the subject to whom the study medication was dispensed
- the date(s), quantity of the study medication dispensed *to* the subject
- the date(s) and quantity of the study medication returned *by* the subject

All records and drug supplies must be available for inspection by the Monitor at every monitoring visit. Subjects will be asked to return all used and unused drug supply containers at the end of the treatment as a measure of compliance.

This inventory must be available for inspection by the Monitor. All supplies, including partially used or empty containers and copies of the dispensing & 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 (Section 6.6).

6.6 Destruction of the IMP

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

Written documentation of destruction must contain the following:

- Identity (batch numbers or subject numbers) of investigational product(s) destroyed
- Quantity of investigational product(s) destroyed
- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)

- Name and signature of responsible person who discarded the investigational product in a hazardous container for destruction

7 SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Adverse Events and Laboratory Abnormalities

7.1.1 Clinical AEs

According to the International Conference of Harmonization [ICH], an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any 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 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:

<u>CTC Grade</u>	<u>Equivalent To:</u>	<u>Definition</u>
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 subject
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 subject 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 subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- Known response pattern to suspected drug
- Disappears or decreases on cessation or reduction in dose
- 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 subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It does not follow a known pattern of response to the suspected drug.
- It does not reappear or worsen when the drug is readministered.

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 subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).
- required in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

The term 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 1).

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 subjects. In this situation, progression is evident in the subject's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

7.1.2 Treatment and Follow-up of AEs

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the CRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the CRF and in the patient's medical record to facilitate source data verification.

At the study treatment completion visit, the investigator should instruct each patient to report to the investigator any subsequent AEs that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should notify the Sponsor of any death, SAE, or other AE of concern occurring at any time after a patient has discontinued study participation if the event is believed to be related to prior study drug treatment or study procedures. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The investigator should report these events on the CRF. If the CRF is no longer available, the investigator should report the event directly to the Sponsor.

7.1.3 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results eform 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 (SAE) 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)

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 Erlotinib Dose Modifications

Reduction/interruption of dosing for adverse events may take place at any time during the study. In the event of any non-dose-limiting toxicity that is:

- Not controlled by optimal supportive care, OR
- Not tolerated due to symptomatology, disfigurement, or interference with normal daily activities, regardless of severity.

The daily dose of erlotinib will be decreased according to the schedule displayed in Table 4.

Table 4 Erlotinib Dose Level Reductions

Starting Dose	First Reduction	Second Reduction
150mg	100mg	50mg

In the event of a rash, dose can be re-escalated when rash is \leq grade 2 (see Figure 3).

Within 2 weeks following a dose reduction, erlotinib related toxicity must improve by at least one NCI-CTC grade and be NCI-CTC Grade \leq 2, or further dose reduction by one level will be required.

Dosing may be interrupted for a maximum of 2 weeks if clinically indicated and if the toxicity is not controlled by optimal supportive medication. Once a patient has had a dose reduction for toxicity, the dose will not be re-escalated except in the case of erlotinib related rash.

7.2.1 Diarrhoea

Occurring in around 50% of patients who receive erlotinib (F. Hoffmann-La Roche Ltd. 2005), diarrhoea is usually transient and, in most cases, can be managed with loperamide (see Table 5).

Recommended regimen: 4 mg loperamide at onset of symptoms, followed by 2 mg every 2–4 hours, until the patient has remained free from diarrhoea for 12 hours.

Patients with severe diarrhoea that is unresponsive to loperamide, or those with associated dehydration, may require dose reduction or interruption.

Appropriate re-hydration should be provided (particularly important for elderly patients, who can rapidly become dehydrated, even with mild diarrhoea).

Table 5 Dosage Modification Criteria and Guidelines for Management of Erlotinib Related Diarrhoea

Toxicity, NCI-CTC Grade	Study Drug Dosage Modification	Guideline for Management
Grade 1	None	Consider Loperamide (4 mg at first onset, followed by 2 mg every 2 – 4 hours until diarrhoea free for 12 hours) and appropriate re-hydration.
Grade 2	None	Loperamide (4 mg at first onset, followed by 2 mg every 2 – 4 hours until diarrhoea free for 12 hours) and appropriate re-hydration.
Grade 3	Interrupt	Interrupt and give appropriate re-hydration, monitor electrolyte balance and renal function until resolution to Grade \leq 1; restart at reduced dose.
Grade 4	Discontinue Study	

7.2.2 Rash

A patient may develop several kinds of dermatological events (including rash) while being treated with HER1/EGFR-specific agents such as erlotinib. In October 2006, an EGFR dermatologic toxicity forum was held in Chicago. This was an international and interdisciplinary meeting, attended by oncologists, oncology nurses, pharmacists, and dermatologists with expertise in the management of cutaneous toxicities associated with EGFRs. The rash management recommendations (see Figures 3 & 4) in this protocol reflected the expert opinions of the forum participants (Lynch et al., 2007), and should not be construed as evidence-based guidelines.

It is important to recognise that the rash typically seen during treatment with erlotinib is pathologically and aetiologically distinct from acne (including steroid-induced acne) and therefore should be managed differently. Information in Figures 3 & 4 provides recommendations on how to recognise and manage the rash associated with erlotinib. This includes a guide to grading the severity of rash, and treatment algorithm developed by medical advisors at Skin Toxicity Forum in Chicago October 2006 (Lynch et al 2007).

In clinical trials, rash was the most common side effect reported with erlotinib, in about 75% of patients. Typically, the rash develops about 7–10 days after the start of treatment, and affects skin areas above the waist. In most patients, the rash is mild (grade 1 or 2). For example, in the pivotal phase III trial (BR.21), only 8% of patients had grade 3 rash, and less than 1% had grade 4 rash. Mild or moderate rash may be managed using topical emollients and corticosteroids, but in a few patients, the rash may be severe enough to warrant dose reduction or withdrawal. There are also many reports of rash resolving spontaneously (without treatment) and reappearing later (during the same treatment regimen).

In this study, when patients come off study treatment, all skin toxicities shall be reviewed and evaluated against causal relationship to erlotinib/placebo, date of first onset and extreme intensity shall be captured on CRF.

Figure 3 Rash Management

- Employ a proactive approach in managing skin rash.
- If patient presents with rash, verify appropriate administration* of drug.

Rash Severity[#]	Intervention
<p>Mild</p> <ul style="list-style-type: none"> • Generally localised • Minimally symptomatic • No impact on activities of daily life (ADL) • No sign of suprainfection 	<p>Continue erlotinib at current dose and monitor for change in severity</p> <p>No treatment OR Topical hydrocortisone** 1-2% cream and/or Clindamycin 1% gel</p>
<p>Moderate</p> <ul style="list-style-type: none"> • Generalised • Mild symptoms (e.g., pruritus, tenderness) • No impact on ADL • No sign of suprainfection 	<p>Continue erlotinib at current dose and monitor for change in severity; Continue treatment of skin rash with the following:</p> <p>Hydrocortisone** 2.5% cream or Clindamycin 1% gel or Pimecrolimus 1% cream PLUS Doxycycline 100 mg bid or Minocycline 100 mg bid</p>
<p>Severe</p> <ul style="list-style-type: none"> • Generalised • Severe symptoms (e.g., pruritus, tenderness) • Significant impact on ADL • Potential for suprainfection 	<p>Continue erlotinib or dose reduction may be necessary and monitor for change in severity; Continue treatment of skin rash with the following:</p> <p>Hydrocortisone** 2.5% cream or Clindamycin 1% gel or Pimecrolimus 1% cream PLUS Doxycycline 100 mg bid or Minocycline 100 mg bid PLUS Systemic steroids (methylprednisolone or prednisolone 30 mg qd [tapered over 30 days])</p> <p>Reassess after 2-4 weeks; if rash worsened, dose interruption or discontinuation may be necessary</p>

- Intervention for rash needs to be maintained even when erlotinib dose is decreased or interrupted, as erlotinib-related rash may have a very long duration.
- Once rash has sufficiently diminished in severity, or resolved, erlotinib treatment may be re-escalated or restarted.

* Patient should be taking the drug on an empty stomach at the same time each day.

** The use of topical steroids should be employed in a pulse manner based on institutional guidelines.

Severity determined based on clinician's assessment and patient's symptoms.

Figure 4 Rash Management cont.

Erlotinib-related rash

- Rash is most likely to occur within 2 weeks after erlotinib treatment. In most cases, rash is mild or moderate, could be managed by topical and/or oral medications without change to erlotinib treatment. Evidence to date suggested that patients who experienced rash might benefit more from erlotinib treatment.
- Rash may resolve spontaneously (without treatment) and/or reappear later (during the same treatment regimen).

General recommendations for erlotinib-related rash:

Avoid

- Sun, heat and humidity can worsen rash.
- Harsh winds, harsh soaps, perfumes and tight-fitting clothes.
- Certain acne medications are not recommended, they may worsen the rash by drying the skin (e.g. topical retinoids) or aggravating dry skin (e.g. benzoyl peroxide).

Make-up

- Rash can be covered with water-based make-up without worsening symptoms. Dermatologist-approved foundations are best (e.g. Dermablend[®]).
- Use skin-friendly liquid cleanser to remove make-up (e.g. Neutrogena[®], Dove[®], or Ivory Skin Cleansing Liqui-Gel[®]).

Moisturiser

- Keep the skin moisturized with thick, alcohol-free lotions and emollients (e.g. Neutrogena Norwegian Formula Hand Cream[®] or Vaseline Intensive Care Advanced Healing Lotion[®]).

Sunlight

- Avoid sunlight (especially skin areas such as face and upper chest), use a sunscreen (SPF 15 or higher), preferably containing zinc oxide or titanium dioxide.

NOTE:

- *All agents should be used according to the prescribing information provided by the manufacturer.*
- The above recommendations are based on: Data on file, Genentech, Inc. Algorithm developed by medical advisors at the Skin Toxicity Forum sponsored by Genentech, Inc., OSI Pharmaceuticals, Inc., and F. Hoffman-La Roche Ltd., in Chicago, III, October 2006; Perez-Soler et al. *The Oncologist* 2005;10:345-356; Lynch et al. *The Oncologist* 2007;12:610-621; Philip et al. *J Clin Oncol.* 2005;23(27):6657-63.

7.2.3 Erlotinib Dosage Interruption/Criteria for Re-challenge

Patients who require an interruption in dosing of > 2 weeks will discontinue erlotinib treatment and be taken off study (except an interruption due to radiotherapy where a maximum of 3 weeks is allowed).

Erlotinib re-challenge after interruption of dosing will occur only if the investigator and the Roche medical monitor agree it is in the best interest of the patient to re-challenge.

Patients for whom erlotinib therapy is interrupted for ≤ 2 weeks for reasons other than erlotinib related AEs may restart erlotinib therapy if the following criteria are met:

- The investigator and the Roche medical monitor agree it is in the best interest of the patient to re-challenge.
- ECOG Performance Status must be 0–2.
- Ocular toxicity must improve to NCI-CTC Grade ≤ 1 (if appropriate).

7.3 Handling of Safety Parameters

7.3.1 Reporting of Adverse Events

7.3.2 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 (as defined in section 7.1.1.3 above), occurring from the enrolment visit (start of study screening procedures), including long term follow-up (LTFU) must be reported to Roche **within 24 hours** of the investigator becoming aware of the event (expedited reporting). The investigator must complete the *SAE Reporting Form [gcp_for000031]* and forward it to the SAE Responsible. All SAEs occurring from the enrolment period must be reported, (start of study screening procedures),

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. Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to investigators at each site and associated IRB/IEC when the following conditions occur:

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

When all subjects at a particular site are off treatment as defined by the protocol:

- only individual SUSAR reports originating in that particular trial will be forwarded to the site and associated IRB/IEC on an expedited basis;

- individual SUSARs considered to be a significant safety issue and/or which result in Roche recommending a change to the Informed Consent Form (ICF), will be reported in an expedited manner to all investigators and IRBs/IECs;
- SUSAR reports originating from other trials using the same IMP will be provided as six monthly SUSAR Reports (SSRs) to investigators and IRBs/IECs where long-term follow-up studies are carried out, unless they are considered significant.

Unrelated Serious Adverse Events must be collected and reported until study closure. This study adheres to the definition and reporting requirements of **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2**. Complete information can be found in Appendix 1.

7.3.3 Reporting of Non-serious events of Special Interest

7.3.4 Pregnancy

A female subject must be instructed to stop taking the test “drug” and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours to the sponsor, using the *Clinical Trial Pregnancy Reporting Form, [gcp_for000023]*. The investigator should counsel the subject, 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. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the investigator.

Pregnancy occurring in the partner of a male subject participating in the study should be reported to the investigator and the sponsor. The partner should be counseled, the risks of continuing the pregnancy discussed, as well as the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

NOTE: The investigator should fill out a *Pregnancy Reporting Form, [gcp_for000023]*, only if the pregnant partner has signed a *Pregnant Partner Data Release Form, [gcp_for000186]*.

7.4 Warnings and Precautions

Erlotinib should only be initiated under the supervision of a physician experienced in the treatment of cancer patients. Erlotinib is contraindicated in patients with severe hypersensitivity to erlotinib or any component of this drug product. **For further information please refer to the Investigator Brochure.**

7.4.1 Drug Interaction

Erlotinib is metabolised by CYP3A4 (see details in IB). Therefore caution should be exercised when erlotinib is co-administered with potent CYP3A4 inhibitors and inducers. Drug interaction studies in healthy volunteers have shown that erlotinib plasma levels are significantly increased by co-administration of the CYP3A4 inhibitor ketoconazole and decreased by co-administration of the CYP3A4 inducer rifampicin. Therefore CYP3A4 inhibitors (conazole antifungals, certain macrolide antibiotics, nefazodone, etc.) may increase erlotinib toxicity. While CYP3A4 inducers (phenytoin, barbiturates,

carbamazepine, rifampin, rifabutin, glucocorticoids, troglitazone, Saint John's wort) probably do not represent a safety concern, but may affect erlotinib efficacy.

1. Concomitant administration of CYP3A4 inhibitors is permitted. Of these, the following are considered to be the most potent inhibitors that may *increase* erlotinib toxicity
 - Systemic antifungals (e.g. ketoconazole, itraconazole, miconazole, etc.).
 - Erythromycin, clarithromycin and troleandomycin.
 - SSRI (e.g., Nefazodone).
2. Concomitant administration of CYP3A4 inducers is permitted. Of these, the following are considered to be of concern as they would decrease levels of erlotinib and hence decrease efficacy but they probably do not represent a safety concern (although antiepileptic levels may need to be monitored for effect on those drugs)
 - Antiepileptics (e.g. carbamazepine, phenobarbital, phenytoin, etc.).
 - Rifampin.
 - Troglitazone.
3. As the degree of effect of erlotinib on other drugs (CYP3A4 substrates) is not known at this time, any CYP3A4 substrate with narrow therapeutic index (TI) should be monitored closely.

7.4.2 Interstitial Lung Disease (ILD)-like Events

From the experience of another EGFR-TKI in Japan, the potential relationship between ILD-like events and the use of EGFR-TKIs is of concern and requires special attention.

In BR.21, the comparison of monotherapy erlotinib with placebo (best supportive care) did not reveal an imbalance between treatment arms for serious ILD-like events. (0.8% in each arm). In the pancreatic cancer study in combination with gemcitabine, the incidence of ILD-like events was 2.5% in the Tarceva plus gemcitabine group versus 0.4% in the placebo plus gemcitabine-treated group.

The overall incidence in patients treated with Tarceva 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 Tarceva 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 the event of acute onset of new or progressive, **unexplained** pulmonary symptoms such as dyspnoea, cough, and fever, erlotinib therapy should be interrupted pending

diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued and appropriate treatment and close follow-up instituted as necessary.

7.4.3 Diarrhoea, Dehydration, Electrolyte Imbalance and Renal Failure

Diarrhoea (sometimes severe) has occurred in patients receiving erlotinib and was usually managed by loperamide; however, reduction in the dose of erlotinib was occasionally necessary. In the event of severe or persistent diarrhoea, nausea, anorexia, or vomiting associated with dehydration, erlotinib therapy should be interrupted and appropriate measures should be taken to treat the dehydration. Some reports of renal failure were secondary to severe dehydration due to diarrhoea, vomiting and/or anorexia while others were confounded by concomitant chemotherapy. In more severe or persistent cases of 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), Tarceva 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.

7.4.4 Hepatotoxicity

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

7.4.5 Gastrointestinal Perforation

Patients receiving Tarceva are at increased risk of developing gastrointestinal perforation, which was observed uncommonly (including some cases with a fatal outcome) (Drug Safety Report 1031686). Patients receiving concomitant antiangiogenic agents, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. Tarceva should be permanently discontinued in patients who develop gastrointestinal perforation.

7.4.6 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. Tarceva treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

7.4.7 Ocular Disorders

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

8 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Primary and Secondary Study Variables

8.1.1 Primary Variable

The primary efficacy variable is duration of progression free survival by RECIST (PFS1), defined as the time from the date of first study dose to disease progression or death whichever occurs first. Disease progression is defined according to the RECIST criteria.

Patients without event (no disease progression or death) will be censored at the date of “last tumor assessment”.

Patients for whom no post-baseline tumor assessments are available are censored at the time of first dose.

The primary PFS analysis will be done after 143 events have occurred.

8.1.2 Secondary Variables

The secondary efficacy variables are:

Progression free survival by investigator’s discretion (PFS2) is defined as the time from the date of first study dose until off-erlotinib PD; the off-erlotinib PD is assessed based on the investigator’s discretion of overall clinical evaluation not limited to RECIST criteria

Objective response rate during first-line therapy is defined as the occurrence of either a confirmed complete (CR) or a partial (PR) best overall response, as determined by the RECIST criteria.

Disease control rate during first-line therapy is defined as stable disease (SD) for 8 weeks or longer, CR plus PR as determined by the RESIST criteria for patients with measurable disease.

Overall survival: This is defined as the time from the date of first study dose to the date of death, regardless of the cause of death. Subjects who were alive at the time of the analysis will be censored at the date of the last follow up assessment. Subjects without follow up assessment will be censored at the day of last dose and subjects with no post baseline information will be censored at the time of first study dose.

Duration of erlotinib treatment in patients who continued erlotinib beyond RECIST PD as measured from the first RECIST PD to the last dose of erlotinib.

8.1.3 Safety

Safety of the treatment will be evaluated by: adverse events, laboratory tests, vital signs, electrocardiogram, chest X ray and performance status.

All subjects who received at least one dose of treatment will be included in the safety evaluation.

8.2 Statistical and Analytical Methods

8.2.1 Primary and Secondary Variables

The primary efficacy endpoint PFS by RECIST (PFS1) is defined as the time from first dose until documented RECIST disease progression or death from any cause at any time, whichever occurs first. Disease progression will be determined by tumor measurements recorded and assessed according to RECIST 1.1. PFS for patients without disease progression or death will be censored at the time of the last tumor assessment, or if no tumor assessments were performed after the baseline visit, at the time of first dose.

Kaplan-Meier methodology will be used to estimate median PFS and 95% confidence interval. Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time.

PFS by investigator's discretion (PFS2) is defined as the length of time from first study dose until Off-erlotinib PD; the Off-erlotinib PD is assessed based on investigator's discretion of overall clinical evaluation not limited to RECIST criteria.

Overall survival is defined as the length of time from randomization until death. It will be analyzed in the same way as PFS.

Objective response rate and disease control rate will be determined along with 95% confidence interval.

8.2.2 The effects of demographic and baseline diseases characteristics on PFS will be examined as exploratory analyses. Subgroup analysis by country will be performed. Hypothesis Testing

This is a single arm study, thus formal hypothesis testing is not required.

8.2.3 Type of Analysis

Per-protocol Population

Per-Protocol (PP) population is defined as those patients who have EGFR mutations confirmed by study designated central laboratory. The primary analysis for efficacy is the PP population.

Intent-to-treat Analysis Population

Intent-to-treat (ITT) population is defined as all patients entered the study. The analysis of the efficacy measures will be repeated using the ITT population. Safety Analysis Population

All patients who receive at least one dose study medication and have at least one post baseline safety assessment performed will be included in the safety analysis.

8.2.4 Interim Analysis

No interim analyses are planned.

8.2.5 Safety Data Analysis

The following safety parameters will be analyzed and presented for all patients in the safety population:

- Adverse events, serious adverse events

- Laboratory parameters
- Vital signs, including ECOG Performance Status
- ECG, Chest X-ray

All adverse events and laboratory parameters will be assessed according to the NCI CTC grading system. For adverse events the most extreme intensity will be used for reporting. Adverse events will be presented in listings and summary tables broken by body system, intensity and relation to trial treatment. Targeted adverse events including rash, interstitial lung disease-like events and diarrhoea will be summarized by overall incidence intensity and relation to trial treatment. Vital signs and ECOG Performance Status will be presented in listings and summary tables. Laboratory values will be presented in listings with flagging of values outside the normal ranges and summarized as change from baseline at each sampling timepoint and NCI –CTC grade.

The extent of exposure to erlotinib will be summarized by duration, starting dose and cumulative dose. In addition, the dose intensity and dose adjustment (reduction and/or interruption) will be calculated for erlotinib.

Withdrawals of patients from study treatment will be reported as listings and summary tables.

No formal testing on safety parameters is foreseen.

8.3 Sample Size

The sample size considerations are based on the following assumptions for the primary endpoint.

- Estimated median PFS is 13 months
- Recruitment over 14 months and maximum follow up of 30 months after first patient recruited.

With these assumptions, a total of 204 patients will be enrolled and 143 (PFS) events would be expected at the end of the follow-up period. These events would represent about 70% of the patients and these data would be considered as sufficiently mature to provide a robust estimate of PFS.

Sample size was estimated using nQuery version 7.0.

9 DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

This is an EDC study.

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

Data for this study will be recorded **via an Electronic Data Capture system EDC using electronic Case Report Forms (CRF)**. It will be transcribed by the site from the paper source documents onto the CRF. **In no case is the eCRF to be considered as source data for this trial.**



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 Roche data base will verify the data and discrepancies will be generated accordingly. These are transferred electronically to the CRF at the site for resolution by the investigator.

Throughout the study the SMT will review data according to the SMT Data Review Plan as described in the Data Quality Plan.

10 REFERENCES

1. American Cancer Society. Cancer Facts & Figures 2002.
2. Janssen-Heijnen ML, Coebergh JW. The changing epidemiology of lung cancer in Europe. *Lung Cancer*. 2003 Sep;41(3):245-58.
3. Johnson DH. Evolution of cisplatin-based chemotherapy in non-small cell lung cancer: a historical perspective and the eastern cooperative oncology group experience. *Chest*. 2000 Apr;117(4 Suppl 1):133S-137S.
4. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical studies. *BMJ*. 1995 Oct 7;311(7010):899-909.
5. Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. *J Clin Oncol*. 1998 Jul;16(7):2459-65.
6. Sandler AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2000 Jan;18(1):122-30.
7. Bonomi P, Kim K, Fairclough D, et al. Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of Paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial. *J Clin Oncol*. 2000 Feb;18(3):623-31.
8. Giaccone G, Splinter TA, Debruyne C, et al. Randomized study of Paclitaxel-cisplatin versus cisplatin-teniposide in patients with advanced non-small-cell lung cancer. The European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *J Clin Oncol*. 1998 Jun;16(6):2133-41.
9. Cardenal F, Lopez-Cabrerizo MP, Anton A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 1999 Jan;17(1):12-8.
10. Pfister DG, Johnson DH, Azzoli CG, et al ; American Society of Clinical Oncology. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol*. 2004 Jan 15;22(2):330-53.
11. Schiller JH, Harrington D, Belani CP, et al; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002 Jan 10;346(2):92-8.
12. Crino L, Scagliotti GV, Ricci S, et al. Gemcitabine and cisplatin versus mitomycin, ifosfamide, and cisplatin in advanced non-small-cell lung cancer: A randomized phase III study of the Italian Lung Cancer Project. *J Clin Oncol*. 1999 Nov;17(11):3522-30.
13. Greco FA, Gray JR Jr, Thompson DS, et al. Prospective randomized study of four novel chemotherapy regimens in patients with advanced nonsmall cell lung

- carcinoma: a minnie pearl cancer research network trial. *Cancer*. 2002 Sep 15;95(6):1279-85.
14. Sculier JP, Lafitte JJ, Paesmans M, et al. Phase III randomized trial comparing moderate-dose cisplatin to combined cisplatin and Carboplatin in addition to mitomycin and ifosfamide in patients with stage IV non-small-cell lung cancer. *Br J Cancer*. 2000 Nov;83(9):1128-35.
 15. Masutani M, Akusawa H, Kadota A, et al. A phase III randomized trial of cisplatin plus vindesine versus cisplatin plus vindesine plus mitomycin C versus cisplatin plus vindesine plus ifosfamide for advanced non-small-cell lung cancer. *Respirology*. 1996 Mar;1(1):49-54.
 16. Comella P, Frasci G, De Cataldis G, et al. cisplatin/Carboplatin + etoposide + vinorelbine in advanced non-small-cell lung cancer: a multicentre randomised trial. Gruppo Oncologico Campano. *Br J Cancer*. 1996 Dec;74(11):1805-11.
 17. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004; 350:2129–39.
 18. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004; 304: 1497–500.
 19. Murray S, Dahabreh IJ, Linardou H, et al. Somatic mutations of the tyrosine kinase domain of epidermal growth factor receptor and tyrosine kinase inhibitor response to TKIs in non-small cell lung cancer: an analytical database. *J Thorac Oncol*. 2008;3: 832–9.
 20. Shepherd FA, Rodrigues PJ, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; 353(2):123-32.
 21. Mok TS, Wu YL, Yu CJ, et al. Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer. *J Clin Oncol* 2009;27:5080-5087.
 22. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *The Lancet Oncology* - 1 June 2010 (Vol. 11, Issue 6, Pages 521-529) DOI: 10.1016/S1470-2045(10)70112-1.
 23. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *New Engl J Med* 2004;350(21):2129-39.
 24. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304(5676):1497-1500.
 25. Paz-Ares L, Sanchez JM, García-Velasco A, et al. A prospective phase II trial of erlotinib in advanced non-small cell lung cancer (NSCLC) patients (p) with mutations

- in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR) *J Clin Oncol* 2006;24(18S):7020.
26. Mok T, Wu YL, Thongprasert S, et al. Phase III, randomised, open-label, first-line study of gefitinib (G) vs carboplatin/paclitaxel(C/P) in clinically selected patients (pts) with advanced non-small cell lung cancer (NSCLC) (IPASS). Presented at: European Society for Clinical Oncology Congress. Stockholm, Sweden, 12–16 September 2008.
 27. Fukuoka M, Wu Y, Thongprasert S, et al. Biomarker analyses from a phase III, randomized, open-label, first-line study of gefitinib (G) versus carboplatin/paclitaxel(C/P) in clinically selected patients (pts) with advanced non-small cell lung cancer (NSCLC) in Asia (IPASS). *J Clin Oncol* 27:15s, 2009 (suppl; abstr 8006).
 28. Kobayashi K, Inoue A, Maemondo M, et al. First-line gefitinib versus first-line chemotherapy by carboplatin (CBDCA) plus paclitaxel (TXL) in non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations: A phase III study (002) by North East Japan Gefitinib Study Group. *J Clin Oncol* 27:15s, 2009 (suppl; abstr 8016).
 29. Paz-Ares L, Sanchez JM, García-Velasco A, et al. A prospective phase II trial of erlotinib in advanced non-small cell lung cancer (NSCLC) patients (p) with mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR) *J Clin Oncol* 2006;24(18S):7020.
 30. Massuti B, Morán T, Porta R, C, et al. Multicenter prospective trial of customized erlotinib for advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Final results of the Spanish Lung Cancer Group (SLCG) trial. *J Clin Oncol* 27:15s, 2009 (suppl; abstr 8023)
 31. Rosell R, Moran T, Queralt C, et al. Screening for Epidermal Growth Factor Receptor Mutations in Lung Cancer. *N Engl J Med* 2009;361:958-67.
 32. Janne PA, Wang XF, Socinski MA, et al. Randomized phase II trial of erlotinib (E) alone or in combination with carboplatin/paclitaxel (CP) in never or light former smokers with advanced lung adenocarcinoma: CALGB 30406. *J Clin Oncol* 28:15s, 2010 (suppl; abstr 7503).
 33. Zhou C, Wu YL, Chen G, et al. Efficacy results from the randomised phase III OPTIMAL (CTONG 0802) study comparing first-line erlotinib versus carboplatin plus gemcitabine in Chinese advanced non small-cell lung cancer patients with EGFR activating mutations. ESMO 2010, abstr LBA13.
 34. Riely GJ, Kris MG, Zhao B, et al. Prospective Assessment of Discontinuation and Reinitiation of Erlotinib or Gefitinib in Patients with Acquired Resistance to Erlotinib or Gefitinib Followed by the Addition of Everolimus. *Clin Cancer Res* 2007;13:5150-5155.



35. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. *J Clin Oncol.* 2009;20;27(12):1999-2006.
36. Chiu CH, Shih YN, Tsai CM, et al. Serum tumor markers as predictors for survival in advanced NSCLC patients treated with gefitinib. *Lung Cancer.* 2007; 57:213-21.

PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

11 ETHICAL ASPECTS

11.1 Local Regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the “Declaration of Helsinki” or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in “Guideline for Good Clinical Practice” ICH Tripartite Guideline [January 1997] or with local law if it affords greater protection to the subject. For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the USA or under US IND, the investigator will additionally ensure adherence to the basic principles of “Good Clinical Practice” as outlined in the current version of 21 CFR, subchapter D, part 312, “Responsibilities of Sponsors and Investigators”, part 50, “Protection of Human Subjects”, and part 56, “Institutional Review Boards”.

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

Written Informed Consent from Subjects:

11.2.1 Main study Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator [if acceptable by local regulations], to obtain signed informed consent from each subject prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

The investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The Case Report Forms (CRFs) for this study contain a section for documenting subject informed consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

For the subject not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the subject and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject and representative have orally consented to participation in the trial, the witness’ signature on the form will attest that the information in the consent form was accurately explained and understood.

If children are old enough to understand the risks and benefits of the study, they should also be informed and should also provide their written assent. With regard to the donation of a specimen(s) by the minor that will be stored in the RCR this same principle will apply. If the minor is not old enough to form an opinion or assess this information, the legal representative/guardian will replace the minor in recognizing his/ her rights and responsibilities until he/ she reaches legal age.

11.2.2 RCR Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable under local regulations), to obtain written informed consent from each individual who has consented to have their samples stored for future research in the RCR after adequate explanation of the aims, methods, objectives and potential hazards. Subjects must receive an explanation that they are completely free to refuse long term storage of their samples for future research and may withdraw his/ her sample at any time and for any reason during the 15 year storage period of the specimen(s). The Informed Consent for an **optional** specimen donation will be incorporated as a specific section into the main Clinical Trial [or Experimental Research study] Informed Consent Form (ICF). A second, separate, specific signature consenting to specimen donation will be required to document the study participant's agreement to provide an optional specimen for long-term storage of their samples for future research; if the participant declines, he/ she will check a "no" box in the appropriate section and not provide a second signature.

The CRF for the associated clinical study contains a page for documenting subject informed consent to the RCR, and this must be completed appropriately.

11.2.3 Death or Loss of Competence of Participant who has donated a specimen(s) that is stored in the RCR

In case the Informed Consent Form and/or the Study Protocol do not provide any specific provisions for death or loss of competence, specimen and data will continue to be used as part of RCR research.

In the event of the death of a participant of a Roche Clinical Trial or Experimental Medicine Research study or if a participant is legally incompetent at the time of the specimen and data procurement, or becomes legally incompetent thereafter, applicable provisions as stated for such situations in the respective Informed Consent Form and/or the Study Protocol shall become effective and be followed accordingly.

Additional procurement of assent from legally incompetent persons and minors shall take place according to local laws and international best practice, as it applies to the specific case

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

The protocol, informed consent and any accompanying material provided to the subject in the U.S. will be submitted by the investigator to an IRB for review. For EEA member states, the sponsor will submit to the Competent Authority and IEC, the protocol and any accompanying material provided to the subject. In both the US and EEA member states,



the accompanying material may include subject information sheets, descriptions of the study used to obtain informed consent and terms of any compensation given to the subject 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 subject after receipt of the IEC/IRB approval must also be submitted by the investigator in the U.S. and by the Sponsor in the 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.

Long term storage of samples in the RCR is contingent on review and approval of the exploratory biomarker assessments and written informed consent by an appropriate regulatory body (depending on the country where the study is performed) and a site's Institutional Review Board (IRB) / Ethics Committee (EC). If a regulatory authority or site's IRB/ EC does not approve the long term storage of samples for the exploratory assessments, the section on biomarker sampling will only be applicable for 5 year storage of samples.

Roche shall also submit an Annual Safety Report once a year to the IEC and Competent Authorities (CAs) according to local regulatory requirements and timelines of each country participating in the study. In the U.S. Roche submits an IND Annual Report to the FDA according to local regulatory requirements and timelines.

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 Clinical Science Leader and Biostatistician.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board 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 subjects, 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. The appropriate IRB/IEC and Regulatory Agencies should be informed accordingly.

14 STUDY DOCUMENTATION, CRFS AND RECORD KEEPING

14.1 Investigator's Files / Retention of Documents

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

The Investigator's Study File will contain the protocol/amendments, CRF/DCS and schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. In addition at the end of the study the investigator will receive the subject data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the Investigator's Study File.

Subject clinical source documents [usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs] would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and subject 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 can not guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and Roche to store these in a sealed container[s] outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

ICH GCP guidelines require that Investigators maintain information in the study subject's records which corroborate data collected on the CRF(s). Completed CRF will be forwarded to Roche.

14.2 Source Documents and Background Data

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

14.3 Audits and Inspections

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

14.4 Electronic Case Report Forms

Data for this study will be captured via an Electronic Data Capture (EDC) system by using eCRFs on a laptop. The data is entered on to the laptop using the off-line mode. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. The investigator will connect on a regular basis, using an analog phone line, and the data will be transferred directly to the Roche database.

For each subject enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those subjects who fail to complete the study [even during a pre-randomization screening period if an eCRF was initiated]. If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

15 MONITORING THE STUDY

It is understood that the responsible Roche monitor [or designee] will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial [CRFs and other pertinent data] provided that subject confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the CRFs 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 subject received the study drug. The monitor should have access to laboratory test reports and other subject 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.

Roche Clinical Repository specimens will at all times be tracked in a manner consistent with Good Clinical Practice, by a quality controlled, auditable and validated Laboratory Information Management System, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in the study protocol and ICF, respectively. Roche monitors and auditors will have direct access to appropriate parts of records relating to subjects participating in this study for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, Institutional Review Board/Independent Ethics Committee (IRB/IEC) review, and regulatory inspections by providing direct access to source data and documents related to the RCR Research Project.

16 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject enrollment log showing codes, names and addresses.

17 CLINICAL STUDY REPORT (CSR)

A clinical study report will be written and distributed to Health Authorities as required by applicable regulatory requirements.

Note: EU Regulation (EC) No.1901/2006, states: For pediatric studies the CSR must be distributed to the applicable Health Authorities within six months of completion of the study.

18 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Roche will comply with the requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

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.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements.

Appendix 1 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 Adverse Event 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 Adverse Event 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, causality can be one of 2 possibilities:

- No (unrelated; equals not drug related).
- Yes (remotely, possibly, probably or definitely drug related).

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



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.

SAEs should be reported by the investigator, within 24 hours of becoming aware of the event, direct to the local Roche Medical Monitor **and** the Roche PDMS-Safety Risk Management Central Operations as detailed below:

PDMS-Safety Risk Management Central Operations

(please fax to only **one** of the three numbers below, alternative numbers are provided in case of transmission problems)

Address	PDMS Central Operations Roche Products Ltd 6 Falcon Way, Shire Park, Welwyn Garden City, Herts, AL7 1TW UK
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Fax 1:	+44 1707 373793
or Fax 2 :	+44 1707 373779
or Fax 3 :	+44 1707 377967
or Fax 4 :	+44 1707 390959

Email:	welwyn.pds-pc@roche.com
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For SAEs, 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 SAE in writing as soon as is practical and in accordance with international and local laws and regulations.

Appendix 2 New Response Evaluation Criteria in Solid Tumors – Version 1.1 – Modified Excerpt From Original Publication with Addition of Supplementary Explanations [1]

1 MEASURABILITY OF TUMOR AT BASELINE

1.1 Definitions

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

1.1.1 Measurable Tumor lesions

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

10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval 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 ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also section 2.2 below on ‘Baseline documentation of target and non-target lesions’ for information on lymph node measurement.

1.1.2 Non-measurable Tumor lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 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, peritoneal spread, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding lesion measurability

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

Bone lesions:

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

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Target lesions: Specifications by methods of measurements

1.2.1 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.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging based evaluation should always be the preferred option.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

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.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the subject at baseline and during study, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor markers, Cytology, Histology: The utilization of these techniques for objective tumor evaluation can not generally be advised but will be dependent on the study design.

2 TUMOR RESPONSE EVALUATION

2.1 Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1.1.1).

2.2 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 (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions. (even if size is greater than 10mm by CT scan).

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 *reproducible in 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 tumor. As noted in section 1.1.1,

pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm 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 tumor. 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, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 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 ≥ 10 mm 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 characterize any objective tumor 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’ (see also section 2.3.4).

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3 Response criteria

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

2.3.1 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 including baseline (nadir). 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.

2.3.2 Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

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 them as 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 and BML (below measurable limit) should be ticked (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 and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked (BML is equivalent to a less than sign <).

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’.

2.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor 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, if applicable, normalization of tumor 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 tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see section 2.3.4) of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

2.3.4 Special notes on assessment of progression of non-target disease

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

2.3.5 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 tumor (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 during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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.

2.4 Evaluation of response

2.4.1 Time Point Response (Overall response)

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

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

Table 1 Time Point Response – Target (w/wo non- target) Lesions

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

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

Table 2 Time Point Response – Non-Target Lesions only

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

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

2.4.2 Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable 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 during study 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.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be “Unable to Assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are indicated as ‘not assessed’, the response for non-target lesions should be “Unable to Assess” (except where there is clear progression). Overall response would be “Unable to Assess” if either the target response or the non-target response is “Unable to Assess” (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Table 3 Best Overall Response when Confirmation is required

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

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

2.4.3 Special notes on response assessment

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

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.

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.

In studies where patients with advanced disease are eligible (i.e. primary disease still or partially present), the primary tumor should be also captured under target or non-target lesions as appropriate. This is to avoid wrong assessments of complete overall response by statistical programs while the primary is still present but not evaluable.

3 REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;**45**:228-47.

Appendix 3 ECOG Performance Status

ECOG PERFORMANCE STATUS

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Reference:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 4 Calculation of Estimated Creatinine Clearance

Calculation of Estimated Creatinine Clearance (Cockroft and Gault)

Cockroft-Gault Formula for females:

Creatinine clearance (mL/min) =

$$[(140 - \text{age}) \times \text{weight (in kg)} \times 0.85] / [72 \times \text{serum creatinine (in mg/dL)}]$$

or

$$[(140 - \text{age}) \times \text{weight (in kg)} \times 0.85] / [0.81 \times \text{serum creatinine (in } \mu\text{mol/L)}]$$

Cockroft-Gault Formula for males:

Creatinine clearance (mL/min) =

$$[(140 - \text{age}) \times \text{weight (in kg)}] / [72 \times \text{serum creatinine (in mg/dL)}]$$

or

$$[(140 - \text{age}) \times \text{weight (in kg)}] / [0.81 \times \text{serum creatinine (in } \mu\text{mol/L)}]$$

Appendix 5 CYP3A4 Substrates, Inhibitors and Inducers

Based on the results of conducted drug drug interaction studies, we recommend caution in using CYP3A4 inhibitors or inducers concomitantly with erlotinib. *Please note that whilst caution and careful monitoring is recommended if the use of these compounds is necessary, usage does NOT exclude the patient from participating in the study.*

Listed on the following page are known substrates, inhibitors and inducers of the CYP3A4.

Generally, systemic antifungals, SSRI, macrolides, grapefruit juice, protease inhibitor drugs (particularly in multiple/chronic doses) should be avoided.

NOTE THAT,

- 1 Of this list, the following are considered to be the most potent inhibitors that **may increase erlotinib toxicity**;
 - Systemic antifungals – (e.g. ketoconazole, itraconazole, miconazole etc.)
 - Erythromycin, clarithromycin and troleandomycin
 - SSRI (e.g. Nefazodone),
 - Grapefruit juice
 - some calcium channel blockers (e.g. verapamil, diltiazem)
- 2 Of this list, the following are considered to be the most common inducers, these are of concern as they would decrease levels of erlotinib and hence decrease efficacy but they probably do not represent a safety concern (although antiepileptic levels may need to be monitored for effect on those drugs)
 - antiepileptics (e.g. carbamazepine, phenobarbital, phenytoin etc.),
 - rifampin,
 - troglitazone
- 3 Significant interactions with the clearance of other CYP3A4 substrates are unlikely. Any CYP3A4 substrate with narrow therapeutic index should be monitored closely.

IN SUMMARY,

- 4 Wherever feasible, known inhibitors and inducers of the CYP3A4 referred to in 1.1 and 1.2 above should be avoided. Any CYP3A4 substrate, with a narrow therapeutic index, used as a concomitant drug should also be closely monitored.

If medically indicated, and no alternative is available, the use of known CYP3A4 substrates (with a narrow therapeutic index), inhibitors and inducers is permitted. IT IS RECOMMENDED THAT IN SUCH CASES THE PATIENT IS CAREFULLY MONITORED.

Table 6 List of CYP3A4 Substrates, Inhibitors and Inducers

Cytochrome P450-3A4 Isoenzyme

Substrates	Inhibitors	Inducers
Alfentanil, Alprazolam, Amitriptyline (minor), Amlodipine, Astemizole, Atorvastatin, Busulfan,	Amiodarone,	
Cannabinoids, Carbamazepine, Cisapride, Clindamycin, Clomipramine, Clonazepam, Cocaine, Cyclobenzaprine, Cyclophosphamide, Cyclosporine,	Cannabinoids, Clarithromycin	Carbamazepine
Dapsone, Dexamethasone, Dextromethorphan, Diazepam (minor), Diltiazem, Disopyramide, Donepezil, Doxorubicin, Dronabinol,		Dexamethasone
Erythromycin, Estrogens, oral contraceptives, Ethosuximide, Etoposide,	Erythromycin	Ethosuximide
Felodipine, Fentanyl, Fexofenadine,	Fluconazole, Fluoxetine, Fluvoxamine Grapefruit Juice	
Ifosfamide, Imipramine, Indinavir, Isradipine, Ketoconazole,	Indinavir, Itraconazole Ketoconazole	
Lansoprazole (minor), Lidocaine, Losartan, Lovastatin, Mibefradil, Miconazole, Midazolam,	Metronidazole, Mibefradil, Miconazole	
Navelbine, Nefazodone, Nelfinavir, Nicardipine, Nifedipine, Nimodipine, Nisoldipine,	Nefazodone, Nelfinavir, Norfloxacin	
Ondansetron,	Omeprazole (slight)	
Paclitaxel, Pravastatin, Prednisone,		Phenobarbital, Phenytoin, Primidone
Quinidine, Quinine,	Quinine	
Rifampin, Ritonavir,	Ritonavir	Rifabutin, Rifampin
Saquinavir, Sertraline,	Saquinavir, Sertraline	
Tacrolimus, Tamoxifen, Temazepam, Terfenadine, Testosterone, Triazolam,	Troleandomycin	Troglitazone
Verapamil, Vinblastine, Vincristine, R-Warfarin		
Zileuton	Zafirlukast	