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

**NCT Number:** NCT01260181

**Document Date:** SAP Version 1: 28 March 2014

# MUTAR

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

**STATISTICAL ANALYSIS PLAN, Version No 1**

| | |
|---|---|
| PROTOCOL NUMBER: | ML25434 |
| STUDY DRUG: | Erlotinib |
| IND NUMBER: | RO0508231 |
| SPONSOR: | Roche Farmacêutica Química, Lda. |
| PLAN PREPARED BY: | [redacted] |
| DATE: | 28 March, 2014 |

**STATISTICAL ANALYSIS PLAN (SAP)**

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

**PROTOCOL VERSION:** 1.5

**PROTOCOL DATE:** 12Feb2014

SAP prepared by:

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Roche Farmacêutica Química, Lda.

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# 1 BACKGROUND

## 1.1 BACKGROUND AND RATIONALE

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

### 1.1.1 Background

Non-small cell lung cancer is the most common cause of cancer death worldwide[1]. In the EU the crude incidence of lung Cancer is 52.5 patients per 100,000 individuals each year with a mortality rate of 48.7 per 100,000/year. Mortality and incidence rates are very similar, due to low survival of these patients[2]. In the developed world lung cancer remains the commonest reason of cancer death in both men and women, although mortality rates for men are dropping[3]. Among men the incidence and mortality rates are 82.5 and 77.0 per 100,000/year, respectively, and for women these rates are 23.9 and 22.3 per 100,000/year, respectively[2]. Non-small cell lung cancer (NSCLC) comprises 80% of reported lung cancer cases and the majority of its new cases are diagnosed in an advanced stage[4,5], once it represents a disease for which there is no established screening. Survival statistics are among the worst for any malignancies, and have not improved in the last years[6]. Indeed, nowadays the median survival for lung cancer is 6–12 months from the time of diagnosis with an overall 5-year survival of 5–10%[3]. Nowadays surgery (lobectomy/pneumonectomy plus mediastinal lymph node dissection) offers the best chance of cure in lung cancer, especially for NSCLC cases[2]. However, only a small part of patients are suitable for curative resection and the majority must rely on non-surgical and adjuvant therapies[3]. For most patients resection was technically unsuitable because of obvious dissemination of disease. Therefore, chemotherapy with palliate purpose to prolong patients' life for few months has been increasingly proved by clinical studies[3]. A common first-line therapy for advanced cases of NSCLC in patients with good performance status (PS) is based on combinations of platinum. Despite the first-line chemotherapy is appropriate, most patients experience disease progression. With regard to second-line systemic treatment (docetaxel, pemetrexed, erlotinib) this may improve the symptoms related to disease and survival of patients[2]. Second-line therapy is administered for disease progression, recurrence, or intolerable adverse effects following administration of initial chemotherapy[7]. In first line, doublet chemotherapy has been found to be superior to single-agent chemotherapy[8]. Platinum-based chemotherapy combined with vinorelbine, gemcitabine or a taxane prolongs survival, improves quality of life and controls symptoms in patients with good performance status. Non-platinum combination

chemotherapy can be considered in patients who are not fit to receive platinum agents. In Second line, in a phase III study, Shepherd and colleagues proved the efficacy of erlotinib against placebo in increasing the survival and reduced symptoms[9]. Erlotinib response rates are higher in non-smokers, women, adenocarcinomas, Asians and patients with EGFR mutations[2]. Several studies show that erlotinib prolongs survival in patients with advanced NSCLC after the failure of first line or second line chemotherapy[9]. In a phase II clinical trial, 57 patients with refractory NSCLC received erlotinib monotherapy and showed a response rate of 12.3% and a median survival of 8.4 months[10]. Based on these results and for a different pharmacological profile, erlotinib was approved by the FDA for the treatment of second and third line NSCLC. Some studies have also shown that mutations in the EGFR gene are associated with response to EGFR TKI[11].

### 1.1.2 Erlotinib (OSI-774; Tarceva®)

Erlotinib is an orally active and potent inhibitor of tyrosine kinase, which acts on the epidermal growth factor receptor (EGFR) developed for the treatment of solid tumours including NSCLC[12]. The recommended daily dose of erlotinib is 150 mg[13].

Erlotinib acts via direct and reversible inhibition of the human EGFR tyrosine kinase, with an IC50 of 2 nM (0.786 ng/mL) in an in vitro enzyme assay, and reduces receptor autophosphorylation in intact tumour cells with an IC50 of 20 nM (7.86 ng/mL)[13].

At nanomolar concentrations, erlotinib blocks Epidermal Growth Factor (EGF)-dependent cellular proliferation and inhibits cell cycle progression in the G1 phase. Selectivity testing against a panel of isolated tyrosine kinase demonstrated that erlotinib is selective for the EGFR[13].

The most frequently-reported adverse events (AEs) associated with single-agent erlotinib are rash (dermatosis), diarrhoea, nausea, fatigue, stomatitis, vomiting, and headache[13]. On the other hand, skin rash was identified as a key indicator of erlotinib trough plasma concentrations[14]. These results support those from previous studies on EGFR inhibitors, which have revealed a similar association between drug steady-state plasma concentrations and the intensity of rash and diarrhoea[15,16]. Laboratory abnormalities, primarily involving changes in liver function tests (elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or bilirubin) are less frequently observed with single-agent erlotinib. These abnormalities occur occasionally in patients treated with erlotinib in combination with either gemcitabine, or carboplatin and paclitaxel[13]. Caution should be used when administering Tarceva to patients with hepatic impairment. Dose reduction or interruption of Tarceva should be considered if severe adverse reactions occur[13,17].

An indication of completed and ongoing clinical studies on erlotinib in NSCLC can be found in the Investigator's Brochure[13].

# 2 STUDY OBJECTIVES

## 2.1 PRIMARY OBJECTIVES

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

## 2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To evaluate progression-free survival (PFS);
- To evaluate the EGFR mutation frequency;
- To evaluate the overall survival (OS);
- To evaluate the erlotinib safety profile (Tarceva®; 150 mg);
- To evaluate response duration.

# 3 STUDY DESIGN

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

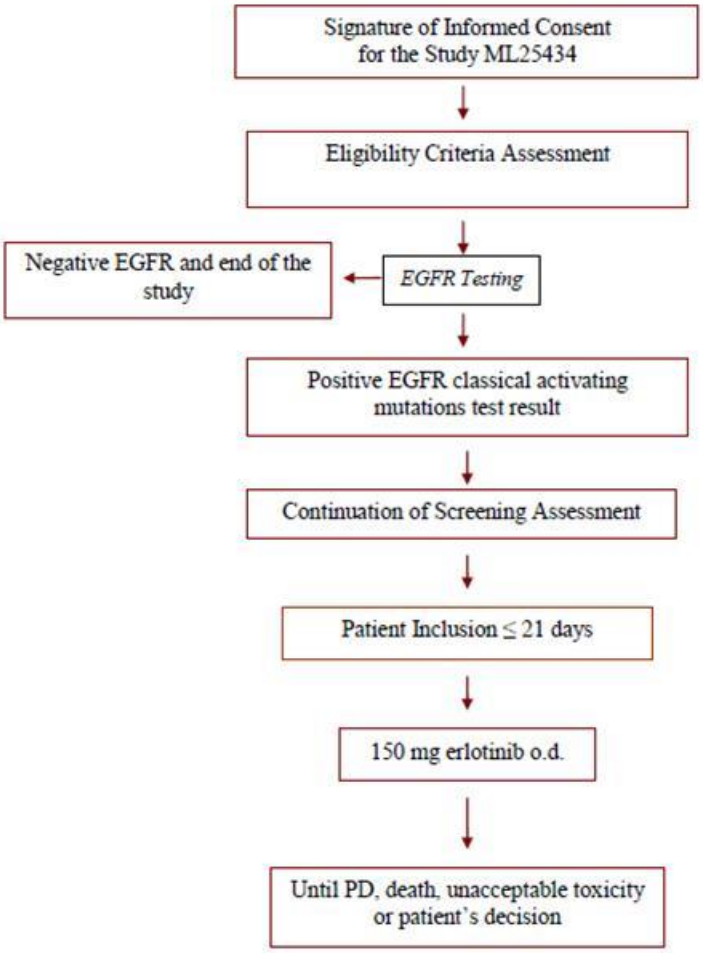


**Figure 1 -** Summary of study design

## 3.1 PROTOCOL SYNOPSIS

The protocol synopsis is in Appendix 1. For additional details, see the Study Flowchart in Appendix 2.

## 3.2 STUDY POPULATION

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

**Inclusion criteria:**

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

1. Patients able and willing to give written informed consent. Consent must be obtained prior to any study-specific procedure.
2. 
    a) Histologically or cytologically documented inoperable, locally advanced or metastatic NSCLC disease;
    b) Patient that presents activating mutations (exon 19 deletion and/or exon 21 substitution L858R ) in the tyrosine kinase domain of EGFR ;
3. Measurable disease, according to RECIST - Response Evaluation Criteria in Solid Tumours).
4. Male or female patients aged ≥ 18 years.
5. Life expectancy ≥ 12 weeks.
6. Adequate haematological and coagulation function as assessed by the investigator.
7. Adequate liver and renal function as assessed by the investigator.
8. Female patients must be postmenopausal (24 months of amenorrhea), surgically sterile or they must agree to use a physical method of contraception. Male patients must be surgically sterile or agree to use a barrier method of contraception. Male and female patients must use effective contraception during the study and for a period of 90 days following the last administration of erlotinib. Acceptable methods of contraception include an established hormonal therapy or intrauterine device for females, and the use of a barrier contraceptive (i.e. diaphragm or condoms) with spermicidal.
9. If applicable, patients with asymptomatic and stable cerebral metastases receiving medical treatment will be eligible for the study. Those patients may have received radiation therapy for their cerebral metastases before the initiation of systemic treatment for non-small-cell lung cancer.
10. Able to comply with the required protocol and follow-up procedures.

**Exclusion criteria**

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

1. Previous treatment with chemotherapy or therapy against EGFR, either with antibody or small molecule (tyrosine kinase inhibitor) for metastatic disease. The administration of neo-adjuvant or adjuvant therapy is allowed as long as it has finalized $\geq$ 6 months before entering the study. Patients can have received radiotherapy as long as the irradiated lesion is not the only target lesion for evaluating response and as long as radiotherapy has been completed before initiating the study treatment (28 days period is recommended). Treatment with an investigational drug agent during the four weeks before enrolment in the study.
2. History of another neoplasm other than carcinoma in situ of the uterine cervix, basal cell skin carcinoma treated adequately, or prostate carcinoma with a good prognosis (Gleason $\leq$ 6) treated radically. History of another neoplasm treated curatively and without evidence of disease in the last 5 years. History of breast cancer and melanoma at any time.
3. Patients with symptomatic cerebral metastases.
4. Known hypersensitivity to erlotinib or any of its excipients.
5. Any significant ophthalmologic abnormality, especially severe dry eye syndrome, keratoconjunctivitis sicca, Sjögren's syndrome, severe exposure keratitis or any other disorder likely to increase the risk of corneal epithelial lesions. (The use of contact lenses is not recommended during the study. The decision to continue to wear contact lenses should be discussed with the patient's treating oncologist and the ophthalmologist.)
6. Use of coumarins (Sintrom®; Varfine®). If the patient requires anti-coagulant therapy, instead of coumarins, the use of a low molecular weight heparin is recommended, whenever clinically possible.
7. Patients with severe hepatic and renal impairment as assessed by the investigator.
8. Evidence of any other disease, neurological or metabolic dysfunction, physical examination or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications.
9. 

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

   b) Patients (male or female) with reproductive potential not willing to use effective method of contraception during the trial and during 90 days after the last erlotinib administration. Oral or injectable contraceptive agents cannot be the sole method of contraception.
10. Patients with pre-existing disease of the lung parenchyma such as lung fibrosis, lymphangitic carcinomatosis.

11. Patients with known infection with HIV, HBV, HCV. Testing is not required in the absence of clinical signs and symptoms suggestive of these conditions.
12. Patients those in the Investigator's opinion are not able to accomplish protocol requirements.
13. Incapacity to take oral medication or previous surgical procedures that affect absorption and imply the need for intravenous or parenteral feeding.

## 3.3 ENDPOINTS

### 3.3.1 Primary efficacy endpoint

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

### 3.3.2 Secondary efficacy endpoints

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

### 3.3.3 Safety outcome endpoints

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

## 3.4 ANALYSIS TIMING

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

# 4 STUDY CONDUCT

## 4.1 RANDOMIZATION ISSUES

Not applicable, since this is a single-arm trial (all patients are assigned to treatment). For each patient enrolled in the study, a sequential number will be attributed (01- 30).

## 4.2 DATA MONITORING

See the study Trial Monitoring Plan.

# 5 STATISTICAL METHODS

## 5.1 DETERMINATION OF SAMPLE SIZE

The sample size was calculated based on the primary variable of the study, objective response rate. Since this proportion is unknown an exploratory sample size of 30 patients was considered to evaluate primary endpoint. This sample size will allow estimating ORR with a margin of error of approximately ±17.5%, for a 95% confidence interval.

Furthermore, approximately 2000 new cases of stage IIIB and IV NSCLC are diagnosed per year in Portugal1 and, based on published data, expected prevalence of EGFR mutation is approximately 10%. With a 95% confidence interval, it was calculated that at least 420 patients will have to be screened to achieve 30 positive cases for the exploratory sample size analysis.

## 5.2 ANALYSIS POPULATIONS

### 5.2.1 Intention to treat (ITT) population

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

### 5.2.2 Per protocol (PP) population

Per protocol population will include all subjects enrolled in the treatment phase of the study without major protocol violations.

The protocol violations and corresponding impact are listed below.

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

### 5.2.3 Safety population

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

## 5.3 ANALYSIS OF STUDY CONDUCT

A descriptive analysis of all study variables will be done. For continuous variables, the mean, standard deviation (SD), median, maximum and minimum will be computed whereas for categorical variables the absolute (n) and relative frequencies (%) will be described.

All analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary, USA).

All derived variables to be used in the analysis are described in Appendix 3.

### 5.3.1 Patient disposition

The number of patients included in this study, as well as the number of screening failures will be described in this section. The reason for study treatment termination will be described (progression of disease, unacceptable toxicity and withdrawal of informed consent or death) together with reason for treatment discontinuation (lost to follow-up, investigator's decision or other reason) through absolute (n) and relative frequencies (%). The number (n) and relative frequency (%) of each study population will be also summarized.

### 5.3.2 Demographics

The age, smoking duration and average number of cigarettes/day if smoker/ex-smoker at the screening visit will be described using median, mean, standard deviation, maximum and minimum.
Gender and smoking habits (non-smoker, smoker or ex-smoker) will be described using absolute (n) and relative (%) frequencies.
Demographic characteristics will be presented considering the ITT population.

### 5.3.3 Childbearing potential/Pregnancy test

For female patients, the childbearing potential and contraception method at the screening visit will be described using absolute (n) and relative (%) frequencies. If a female patient is of childbearing potential, the incidence of pregnancy tests performed and respective result (positive/negative) will be evaluated.

The number of men who uses a contraception protection, or who are surgically sterilized or naturally sterile or abstinent or have a partner surgically sterile will also be assessed using frequencies.
The childbearing potential/pregnancy test information will be collected at the screening visit, baseline visit and at the end of study treatment.
Results will be presented considering the ITT population.

### 5.3.4 Medical history

#### 5.3.4.1 NSCLC Diagnosis

The disease duration (in years) at the screening visit will be described using median, mean, standard deviation, maximum and minimum. The diagnosis technique (histology/cytology), pathology results (adenocarcinoma, bronchoalveolar carcinoma, large cell carcinoma, squamous cells carcinoma, mixed cell type or other), TNM classification (T, N and M)) and location of metastatic disease (adrenal glands, liver, brain, bone or other) will also be described using absolute (n) and relative (%) frequencies.

#### 5.3.4.2 Co-morbidities

The number of patients having any co-morbidity at the screening visit will be assessed. For patients with co-morbidities, the frequency of patients in grade 1 to 5, or with mild, moderate, severe, life threatening or disabling severity or death related will be described.

Results on medical history will be presented considering the ITT population.

### 5.3.5 ECOG performance status

The absolute (n) and relative (%) frequencies of patients with performance status information at each visit will be assessed as well as its respective result using median, mean, standard deviation, minimum and maximum.
Results will be presented considering the ITT population.

### 5.3.6 Concomitant medications

The absolute (n) and relative (%) frequencies of patients taking any concomitant medication will be assessed.
Concomitant medication will be presented considering the ITT population.

### 5.3.7 Tumour assessment

The absolute (n) and relative (%) frequencies of patients with a pre-existing CXR, a chest and upper abdomen CT Scan or MRI, an isotope bone scan, a brain CT Scan or a brain MRI will be described for each visit. For patients with any of these exams performed, the proportion of patients with abnormal clinically relevant exam results will be evaluated. Tumor assessment using the RECIST criteria (Appendix 5) will be carried at baseline, within +/- 5 days of the 8-weekly assessments and at the end of study treatment visit. For tumor assessments completed outside the scheduled time, results will be analyzed as part of the nearest scheduled visit.
Results on tumour assessment will be presented considering the ITT population.

### 5.3.8 Clinical response (RECIST criteria)

At each planned time point, the overall response (complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD)) will be assessed for each patient, taking into account both target and non-target lesions, as per RECIST criteria. This will be summarized as the percentage of patients reaching each level of response at that time point. At the end of the study treatment, best overall response will be determined for all patients and presented as percentages of patients with each level of response.
In addition, for each study visit the number of patients with lesions evaluated through CT Scans, MRIs or Spiral CT Scans will be described, as well as the percentage of patients with target and non-target lesions placed at the brain, liver, lymph nodes, bones, skin, peritoneum, lung or other location.
Results on clinical response will be presented considering the ITT population.

### 5.3.9 Efficacy analysis

In this trial, the efficacy endpoints will be analyzed for ITT and PP population. The ITT analysis will be considered as the primary analysis.

#### 5.3.9.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the objective response rate (ORR) defined by the number of patients with complete response (CR) or partial response (PR) as the best overall response during the treatment period divided by the total number of patients based on diagnostic imaging according to RECIST 1.1 (see Appendix 5). The ninety five percent (95%) confidence interval will be estimated for the ORR.

### 5.3.9.2 Secondary Efficacy Endpoints

The secondary efficacy variables include:

- Progression-free survival (PFS), defined as the time from baseline visit to the date of first occurrence of disease progression or death for any cause while the patient was under study or during the prolonged follow-up period. PFS will be summarized as median time and will be estimated using the Kaplan-Meier method. Ninety five percent (95%) confidence interval will be estimated for median time to PFS.

- Overall survival (OS), defined as the time from the first dose of erlotinib to the date of death due to any cause while the patient was under study or during the prolonged follow-up period. Overall survival variable will be summarized as median time to OS and will be estimated using the Kaplan-Meier method. 95% confidence interval will be estimated for median time to OS. The date of first dose is not captured in the study CRF. Therefore, for this endpoint it will be assumed that the patient will take the first dose at the day of the baseline visit.

- Epidermal growth factor receptor (EGFR) mutation frequency. The presence of EGFR mutation (exon 19 deletion and/or exon 21 substitution L858R) in the study population will be presented as the relative frequency of those mutations among the total screened patients. A 95% confidence interval will be estimated for this value using binomial distribution.

- Response duration, defined as the time of initial response (CR/PR whichever is first recorded) until documented tumor progression. Response duration will be summarized as median time and will be estimated using the Kaplan-Meier method. Ninety five percent (95%) confidence interval will be estimated for median time to response duration.

### 5.3.9.3 Exploratory Efficacy analysis

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

### 5.3.10 Safety analysis

Safety endpoints will be presented considering the safety population.

### 5.3.10.1 Drug dispensing and accountability

During the treatment period, the number of patients whose study medication was dispensed will be evaluated together with the frequency of patients starting the study with doses of 150mg, 100mg or 50mg, the median (range) duration of study drug dispensability, and the mean (SD)/median (range) number of respective units (tablets) dispensed. Moreover, the percentage of patients who kept the same initial dose until the end of study treatment and who had to change dose will be calculated as well as the mean of the weighted average doses of each patient (the weights being the time a patient was on each dose).

At the end of study treatment, the mean (SD) compliance ratio for each patient will be derived, and the respective percentage of compliant patients assessed. Furthermore, a patient will be deemed compliant if the compliance ratio is at least 80%.

### 5.3.10.2 Physical examination

The absolute (n) and relative (%) frequencies of patients who perform a physical examination at each visit will be evaluated. The frequency of abnormal results in the examination of the skin, nails, thorax, abdomen, extremities, head, genital, neurological, temperature or other physical examination will be described.

### 5.3.10.3 ECG

The absolute (n) and relative (%) frequencies of patients who perform an ECG at the screening visit, and every time that is clinically indicated will be described, as well as the frequency of abnormal clinically relevant ECGs results for each visit and for total study duration.

### 5.3.10.4 Laboratory data

Laboratory assessment will be carried out at the screening visit and all visits during the treatment period. For the following laboratory parameters:

1) Hematology (hemoglobin, leucocytes, neutrophils, platelets),
2) Coagulation (prothrombin time, activated partial thromboplastin (aPTT), international normalized ratio (INR – only at the screening visit) and
3) Biochemistry (urea, glucose, AST, ALT, creatinine clearance (if indicated), serum creatinine, calcium, sodium, potassioum, chloride, LDH, alkaline phosphatase, total bilirubin)

the percentage of patients with abnormal clinically relevant values will be assessed.

Laboratory will be summarized in shift from baseline tables.

#### 5.3.10.5 Adverse events

Adverse event (AE) data will be presented in frequency tables (overall, by grade (1, 2, 3, 4, or 5), by severity (mild, moderate, severe, life threatening or disabling or death related), by relationship (unrelated, remote relation, possible relation or probable relation) and by action taken (dose changed, interrupted, withdrawal or none). In tables showing the incidence of adverse events, subjects who experienced the same event on more than one occasion are counted only once in the calculation of the event frequency.

For selected events of particular interest, such as Stevens-Johnson syndrome and interstitial lung disease, summary tables will be presented for time to first onset of the event and for the total number of episodes. Every occurrence of an event in any subject will be counted in the total number of episodes but successive reports of an identical event in the same phase (treatment, follow-up) will be combined (concatenated) into a one episode if the end date of the earlier event was the same as the start date of the later event, or if the end date of the earlier event was missing.

A listing of adverse events by patient, whose adverse events led to withdrawal of study treatment or to dose modification will be done. In case of deaths, a brief narrative describing each death will be done.

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

### 5.3.11 Subsequent therapy for NSCLC

In the safety follow-up and off-study visits, the frequency of patients who continue treatment for NSCLC with subsequent therapies will be assessed. For the patients taking subsequent therapies, the therapeutic line and treatment will be further described using absolute (n) and relative (%) frequencies. Results on subsequent therapy for NSCLC will be presented considering the safety population.

## 5.4 MISSING DATA

Incomplete dates will be handled as stated in Appendix 4. All other missing values will be individually omitted from the analyses.

## 5.5 INTERIM ANALYSES

Interim analysis will include the following descriptive analyses:

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

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

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

Interim analysis will be conducted following the methodology/assumptions considered in section 5.3.

# 6 STATISTICAL TABLES

## 6.1 PATIENT DISPOSITION

Patient disposition will be presented as described in **Table 1** of Appendix 6.

## 6.2 DEMOGRAPHICS

Demographic characteristics will be presented as described in **Table 2** of Appendix 6.

## 6.3 CHILDBEARING POTENTIAL/PREGNANCY TEST

Results of the childbearing potential/pregnancy test will be presented as described in **Table 3** of Appendix 6.

## 6.4 MEDICAL HISTORY

Results on medical history will be presented as described in **Table 4** and **Table 5** of Appendix 6.
By-patient listing of co-morbidities will be presented in **Listing 1** of Appendix 7.

## 6.5 ECOG PERFORMANCE STATUS

ECOG performance status data will be presented in **Table 6** of Appendix 6.
By-patient listing of ECOG results will be presented in **Listing 2** of Appendix 7.

## 6.6 CONCOMITANT MEDICATIONS

Concomitant medications will be presented in **Table 7** of Appendix 6.
By-patient listing of concomitant medications will be presented in **Listing 3** of Appendix 7.

## 6.7 TUMOUR ASSESSMENT

Results of tumour assessment will be presented as described in **Table 8** of Appendix 6.

## 6.8 CLINICAL RESPONSE (RECIST CRITERIA)

Results of the clinical response according RECIST criteria will be presented in **Table 9** of Appendix 6.

## 6.9 EFFICACY ANALYSIS

### 6.9.1 Primary Efficacy analysis

Results of the primary efficacy analysis will be presented for ITT population in **Table 10** of Appendix 6 and PP population in **Table 11** of Appendix 6.

### 6.9.2 Secondary Efficacy analysis

Results of the secondary efficacy analysis will be presented in, **Table 12** to **Table 19** of Appendix 6 and in **Figure 2** to **Figure 4**.

*[Insert figure]*

**Figure 2 –** Kaplan-Meier curve for progression free survival – ITT population

*[Insert figure]*

**Figure 3 –** Kaplan-Meier curve for overall survival – ITT population

*[Insert figure]*

**Figure 4 –** Kaplan-Meier curve for response duration – ITT population

### 6.9.3 Exploratory Efficacy analysis

Results of progression free survival by exon 19 and 21 will be presented in **Table 20** and **Table 21** of Appendix 6 and in **Figure 5**.

*[Insert figure]*

**Figure 5 –** Kaplan-Meier curve for progression free survival by exon 19 and 21 – ITT population

## 6.10 SAFETY ANALYSIS

### 6.10.1 Drug dispensing and accountability

Results on the drug administration will be presented in **Table 22** of Appendix 6.

### 6.10.2 Physical examination

Physical exam findings will be presented in **Table 23** of Appendix 6.

### 6.10.3 ECG

Electrocardiogram findings will be presented in **Table 24** of Appendix 6.

### 6.10.4 Laboratory data

Hematology, coagulation, biochemistry results will be presented in **Table 25, Table 26** and **Table 27**, respectively, of Appendix 6.

### 6.10.5 Adverse events

Adverse events will be described in **Table 28** to **Table 38** of Appendix 6.
By-patient listing with data about adverse events will be presented in **Listing 4** of Appendix 7.

## 6.11 SUBSEQUENT THERAPY FOR NSCLC

Results on subsequent therapy for NSCLC will be present in **Table 39** of Appendix 6.

## 6.12 INTERIM ANALYSIS

The interim analysis will include the analyses described in the following sections: 6.2 Demographics, 6.4 Medical history, 6.5 ECOG performance status, 6.8 Clinical response (RECIST criteria), 6.9 Efficacy analysis, 6.10.1 Drug dispensing and accountability (only reduction in starting dose and compliance) and 6.10.5 Adverse events (Table 29 to Table 34, Table 36 and Table 39).

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# Appendix 1: Protocol Synopsis

**SINOPSES OF AIMS PROTOCOL NUMBER: ML25434**

| | | | |
|---|---|---|---|
| TITLE | Phase II, open-label study of erlotinib (Tarceva®) treatment in patients with locally advanced or metastatic non-small cell lung cancer who present activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor. | | |
| SPONSOR | Roche Farmacêutica Química, Lda | CLINICAL PHASE | II |
| INDICATION | Locally advanced or metastatic non-small cell lung cancer (NSCLC). | | |
| OBJECTIVES | **Primary**:<br>Objective response rate (ORR) of erlotinib (Tarceva®; 150 mg) in patients with locally advanced or metastatic stage non-small-cell lung cancer (NSCLC), who have not received previous chemotherapy for their disease and who present activating mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR).<br><br>**Secondary**:<br>• Progression-free survival (PFS),<br>• Overall survival (OS),<br>• Safety profile,<br>• Evaluate the EGFR mutation frequency in the study population | | |
| TRIAL DESIGN | Open-label, multi-centre Phase II study. | | |
| NUMBER OF PATIENTS | 30 patients | | |
| TARGET POPULATION | Patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC who have not received previous chemotherapy for their disease and who present activating mutations in the TK domain of the EGFR. | | |
| INCLUSION CRITERIA | 1. Patients able and willing to give written informed consent. Consent must be obtained prior to any study-specific procedure.<br>2. a) Histologically or cytologically documented inoperable, locally advanced or metastatic NSCLC disease;<br>b) Patient that presents activating mutations in the tyrosine kinase domain of EGFR (Exon 19 deletion and/or exon 21 substitution L858R );<br>3. Measurable disease, according to RECIST - Response Evaluation Criteria in Solid Tumours).<br>4. Male or female patients aged ≥ 18 years.<br>5. Life expectancy ≥ 12 weeks.<br>6. Adequate haematological and coagulation function as assessed by the investigator. | | |

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| | 7. Adequate liver and renal function as assessed by the investigator.<br>8. Female patients must be postmenopausal (24 months of amenorrhea), surgically sterile or they must agree to use a physical method of contraception. Male patients must be surgically sterile or agree to use a barrier method of contraception. Male and female patients must use effective contraception during the study and for a period of 90 days following the last administration of erlotinib. Acceptable methods of contraception include an established hormonal therapy or intrauterine device for females, and the use of a barrier contraceptive (i.e. diaphragm or condoms) with spermicidal.<br>9. If applicable, patients with asymptomatic and stable cerebral metastases receiving medical treatment will be eligible for the study. Those patients may have received radiation therapy for their cerebral metastases before the initiation of systemic treatment for non-small-cell lung cancer.<br>Able to comply with the required protocol and follow-up procedures |
| EXCLUSION CRITERIA | 1. Previous treatment with chemotherapy or therapy against EGFR, either with antibody or small molecule (tyrosine kinase inhibitor) for metastatic disease. The administration of neo-adjuvant or adjuvant therapy is allowed as long as it has finalized $\geq$ 6 months before entering the study. Patients can have received radiotherapy as long as the irradiated lesion is not the only target lesion for evaluating response and as long as radiotherapy has been completed before initiating the study treatment (28 days period is recommended). Treatment with an investigational drug agent during the four weeks before enrolment in the study.<br>2. History of another neoplasm other than carcinoma in situ of the uterine cervix, basal cell skin carcinoma treated adequately, or prostate carcinoma with a good prognosis (Gleason $\leq$ 6) treated radically. History of another neoplasm treated curatively and without evidence of disease in the last 5 years. History of breast cancer and melanoma at any time.<br>3. Patients with symptomatic cerebral metastases.<br>4. Known hypersensitivity to erlotinib or any of its excipients. |

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| | 5. Any significant ophthalmologic abnormality, especially severe dry eye syndrome, keratoconjunctivitis sicca, Sjögren's syndrome, severe exposure keratitis or any other disorder likely to increase the risk of corneal epithelial lesions. (The use of contact lenses is not recommended during the study. The decision to continue to wear contact lenses should be discussed with the patient's treating oncologist and the ophthalmologist.)<br>6. Use of coumarins (Sintrom®; Varfine®). If the patient requires anti-coagulant therapy, instead of coumarins, the use of a low molecular weight heparin is recommended, whenever clinically possible.<br>7. Patients with severe hepatic and renal impairment as assessed by the investigator.<br>8. Evidence of any other disease, neurological or metabolic dysfunction, physical examination or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications.<br>9. a) Positive urine pregnancy test in women of childbearing potential. Female patients should not be pregnant or breast-feeding.<br>b) Patients (male or female) with reproductive potential not willing to use effective method of contraception during the trial and during 90 days after the last erlotinib administration. Oral or injectable contraceptive agents cannot be the sole method of contraception.<br>10. Patients with pre-existing disease of the lung parenchyma such as lung fibrosis, lymphangitic carcinomatosis.<br>11. Patients with known infection with HIV, HBV, HCV. Testing is not required in the absence of clinical signs and symptoms suggestive of these conditions.<br>12. Patients those in the Investigator's opinion are not able to accomplish protocol requirements.<br>Incapacity to take oral medication or previous surgical procedures that affect absorption and imply the need for intravenous or parenteral feeding. |
| LENGTH OF STUDY | This study is event-driven, with a recruitment period that will last until the end of March 2012 or until the number of patients aimed for the protocol (30) is achieved, whatever occurs first. Patients are to be treated until disease progression, unacceptable toxicity, death or patient request for discontinuation. |
| END OF STUDY | The study will end when the last patient has stopped erlotinib therapy and completed their last safety follow-up visit (28 days after last study drug administration). For all |

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| | patients who have discontinued study drug treatment and are alive, information on survival will be collected. |
| INVESTIGATIONAL MEDICINAL PRODUCT(S) DOSE/ ROUTE/ REGIMEN | Patients will be dosed daily with 150 mg erlotinib taken orally until disease progression or unacceptable toxicity. Dose reduction will be allowed according to protocol (Section 6.) |
| ASSESSMENTS OF:<br>- EFFICACY | **Primary Endpoint**:<br>• Objective Response Rate (ORR).<br><br>**Secondary Endpoints**:<br>• Progression Free Survival,<br>• Overall Survival (OS),<br>• Safety profile,<br>• EGFR mutation frequency. |
| - SAFETY | All evaluations will be performed accordingly with the Schedule of Assessments. If clinically indicated, more evaluations could be performed. All adverse events (AEs) will be assessed using the National Cancer Institute Common Terminology Criteria for AEs (NCI CTC-AE) version 4.0. The incidence of serious adverse events (SAEs) and non-SAEs related to erlotinib therapy will be determined. Additional information about AEs of special interest (serious and non-serious) such as Stevens-Johnson syndrome and interstitial lung disease (IDL)-like events will be collected. Information about laboratory exams (haematology, biochemistry and coagulation), ECG and physical examination will be also collected. |
| - EGFR Mutation analysis | If patients are deemed eligible to participate in the study by the investigator, a surgical fragment or biopsy formalin-fixed, paraffin-embedded or a tumour material obtained through aspiration cytology fixed and paraffin-embedded in a cell-block, must be sent to the Central Laboratory [redacted]. If activating mutations (exons 19 and/or 21 mutations) in the TK domain of EGFR gene are identified, patients are eligible to participate in the study. |
| STATISTICAL CONSIDERATIONS<br>- STATISTICAL METHODS | **Efficacy Analyses**:<br>The primary and secondary efficacy analyses will be performed on the intent-to-treat population, defined as all subjects who are enrolled to the treatment phase of the study, regardless if they completed treatment.<br>For ORR 95% confidence interval will be estimated.<br>PFS and OS will be estimated and presented as median time to PFS and OS trough Kaplan-Meier method. 95% confidence intervals will be estimated for this parameters.<br>EGFR expression will be presented as a percentage and 95% confidence intervals will be estimated for this value. |

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| - SAMPLE SIZE CONSIDERATION | **Safety Analyses**:<br>All safety parameters will be summarized and presented in tables based on the safety population.<br>AE data will be presented in standard frequency tables (overall and by intensity) by body system. All AEs and laboratory variables will be assessed according to the NCI CTC-AE version 4.0 grading system.<br><br>The sample size was calculated based on the primary variable of the study, objective response rate. Since this proportion is unknown an exploratory sample size of 30 patients was considered to evaluate primary endpoint. This sample size will allow estimating ORR with a margin of error of approximately ±17.5%, for a 95% confidence interval.<br><br>Furthermore, approximately 2000 new cases of stage IIIB and IV NSCLC are diagnosed per year in Portugal1 and, based on published data, expected prevalence of EGFR mutation is approximately 10%. With a 95% confidence interval, it was calculated that at least 420 patients will have to be enrolled to be tested to achieve 30 positive cases for the exploratory sample size analysis. |

# Appendix 2: Study Flowchart

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

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

[a] Urine or blood.

[b] Including an ophthalmologic examination if clinically indicated.

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

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

suspicion of disease progression based on clinical or laboratory findings, a tumour assessment should be performed as soon as possible, before the next scheduled evaluation.

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

[f] Subsequent therapy for all patients.

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

[h] or as appropriate.

[i] Drug returning and final accountability.

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

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

# Appendix 3: Derived Variables

The following variables will be derived:

**Screening visit**

**Age:** The difference between the screening visit date and the patient's birth date, in whole years.

**Duration of disease:** The difference between the screening visit date and the date of NSCLC diagnosis, in whole years.

**Smoking duration (in years)**: For ex-smokers is the difference between the start and stop year (in years) of smoking and for smokers is the difference between the start year and the screening visit year.

**Stage TNM**: a categorical variable will be obtained. The following criteria will be considered:

Occult Carcinoma – TX, N0, M0;

Stage 0 – Tis N0 M0;

Stage IA – T1a N0 M0;

Stage IB – T1b N0 M0;

Stage IIA – T2b N0 M0 **or** T1a N1 M0 **or** T1b N1M0 **or** T2a N1 M0;

Stage IIB – T2b N1 M0 **or** T3 N0 M0;

Stage IIIA – T1a N2 M0 **or** T1b N2 M0 **or** T2a N2 M0 **or** T2b N2 M0 **or** T3 N1 M0 **or** T3 N2 M0 **or** T4 N0 M0 **or** T4 N1 M0;

Stage IIIB – T1a N3 M0 **or** T1b N3 M0 **or** T2a N3 M0 **or** T2b N3 M0 **or** T3 N3 M0 **or** T4 N2 M0 **or** T4 N3 M0;

Stage IV – Any T, any N and M1a **or** Any T, any N and M1b.

**Treatment period**

**Response duration**: It will be measured from the time of initial response (CR/PR whichever is first recorded) until documented tumor progression (in weeks).

**Best overall response:** a categorical variable will be obtained, defined as the best response across all time points, according to RECIST 1.1, until end of study treatment. The following criteria will be considered:

Complete response – Patients who presented at least one complete response;

Partial response – Patients who not presented a complete response and presented at least one partial response;

Stable disease – Patients who not presented response (complete or partial) and presented at least one stable disease;

Progression disease – Patients who not presented response or stable disease and presented progression disease;

Inevaluable – All assessments are inevaluable.

**Objective response:** A dichotomous variable (yes/no) will be calculated. Patients who presented complete response or partial response as the best overall response will be classified in “yes”. Otherwise patients will be classified in “no”.

**Event PFS**: A dichotomous variable (yes/no) will be calculated. Patients who presented progression disease or death for any cause will be classified in “yes”. Otherwise patients will be classified in “no”.

**Time PFS**: Time between baseline visit and date of first occurrence of disease progression or death for any cause (in weeks) while the patient was under study or during the prolonged follow-up period. In patients where disease progression or death from any cause was not observed, the time will be censored at the date of last visit or last contact with the patient.

**Time overall survival:** The time from the first dose of erlotinib (assumed to be baseline visit) to the date of death due to any cause (in weeks). For patients alive at the end of the follow-up period, the time was censored at the date of last visit or last contact with the patient.

**Medication and adverse events**

**Duration of adverse event:** The interval between the start and end or patient worsened in severity or death dates of the adverse event in days.

**Time to first onset (Interstitial lung disease)**: Time between baseline visit and first occurrence of Interstitial lung disease, in weeks, within patients with this adverse event.

**Time to first onset (Stevens-Johnson syndrom)**: Time between baseline visit and first occurrence of Stevens-Johnson syndrom, in weeks, within patients with this adverse event.

**Duration of study drug dispensability**: The interval between the dispensed medication date at baseline and the returned medication date at the end of study treatment visit in weeks.

**Drug compliance**: The ratio of used units (tablets) (dispensed at a visit) to number of days between visits. In case the prescribed dose is 50mg, the denominator of this ratio will be multiplied by two.

**Weighted average doses**: the weighted average doses of each patient will be calculated according to the following formula

$$\frac{(150mg \times days\ on\ dose\ 150mg) + (100mg \times days\ on\ dose\ 100mg) + (50mg \times days\ on\ dose\ 50mg)}{total\ number\ of\ days\ taking\ medication}$$

**Study populations**

**ITT:** A dichotomous variable (yes/no) will be calculated. Patients who are enrolled to the treatment phase of the study (baseline visit) will be classified in “yes”. Otherwise patients will be classified in “no”.

**PP:** A dichotomous variable (yes/no) will be calculated. Patients who are enrolled to the treatment phase of the study (baseline visit) and without major protocol violations will be classified in “yes”. Otherwise patients will be classified in “no”.

**Safety:** A dichotomous variable (yes/no) will be calculated. Patients who received at least one dose of study medication will be classified in “yes”. Otherwise patients will be classified in “no”.

# Appendix 4: Handling incomplete dates

**Birth dates**

If only the year is known, the complete date will be assumed to be July 1st of the given year. If both month and year are known, the complete date will be assumed to be the 15th of the given month.

**Death dates**

If both month and year are known, the complete date will be assumed to be the 1st of the given month. If only the year is known, the complete date will be:

- the date of last visit or last contact with the patient, if the year of death is equal to the year of last contact
- the 1st day of the year, if the year of death is higher than the year of last contact.

**Adverse events**

*Start date*

If only the year is known, the complete date will be assumed to be January 1st of the given year. If both month and year are known, the complete date will be assumed to be the 1st of the given month.

*End date*

If only the year is known, the complete date will be assumed to be December 31st of the given year. If both month and year are known, the complete date will be assumed to be the last day of the given month.

# Appendix 5: The RECIST Criteria for Tumor Response

**Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1**

**Quick Reference (http://ctep.cancer.gov/guidelines/recist.html)**

**Measurability of tumor at baseline**

**1. Definitions**

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

1.1. Measurable

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

• 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).

• 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

• 20 mm by chest X-ray.

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

**1.2.Non-measurable**

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

**1.3.Special considerations regarding lesion measurability**

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

Bone lesions:

• Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

• Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CTor MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

• Blastic bone lesions are non-measurable.

Cystic lesions:

• Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

• 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

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

**2. Specifications by methods of measurements**

**2.1. Measurement of lesions**

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

**2.2. Method of assessment**

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using 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. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

**Tumor response evaluation**

1. Assessment of overall 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. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2. Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid 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, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm·30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis P10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective 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'. In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

**3. Response criteria**

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

**3.1. Evaluation of target lesions**

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

**3.2. Special notes on the assessment of target lesions**

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report themas being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as

lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

**3.3. Evaluation of non-target lesions**

This section provides the definitions of the criteria used to determine the 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 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 of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

**3.4. Special notes on assessment of progression of nontarget disease**

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall 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 quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in 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.

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

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

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

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

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

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

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

**4. Evaluation of best overall response**

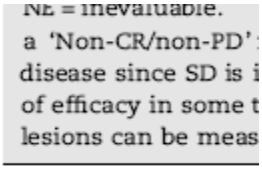
The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment

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

**4.1. Time point response**

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

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


NE = inevaluable.
a 'Non-CR/non-PD'
disease since SD is i
of efficacy in some t
lesions can be meas

**4.2. Missing assessments and inevaluable designation**

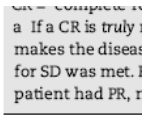
When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the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

**4.3. Best overall response: all time points**

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

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

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


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

**4.4. Special notes on response assessment**

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

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PETand biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

**4.5. Frequency of tumor re-evaluation**

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment)

and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

**4.6. Confirmatory measurement/duration of response**

**4.6.1. Confirmation**

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

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

**4.6.2. Duration of overall response**

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

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

**4.6.3. Duration of stable disease**

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

# Appendix 6: Statistical Tables

**Table 1 –** Patients' disposition

| | **Total (n=xx)** |
|---|---|
| **Patients eligible for study treatment, n(%)** | |
| Yes | |
| No | |
| Total | |
| **Patient complete the treatment as per protocol, n(%)** | |
| Yes | |
| No | |
| Total | |
| **Reason for study treatment termination[a)], n (%)** | |
| Progression of disease | |
| Unacceptable toxicity | |
| Withdrawal of informed consent | |
| Death | |
| Total | |
| **Reason for study treatment descontinuation[a)], n (%)** | |
| Lost to follow-up | |
| Investigator's decision | |
| Other | |
| Total | |
| **Study populations, n (%)** | |
| PP | |
| Safety | |

a) Calculated for patients who received at least one treatment.

**Table 2 –** Demographics – ITT population

| | **Total (n=xx)** |
|---|---|
| **Gender, n (%)** | |
| Male | |
| Female | |
| Total | |
| **Age (years)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |
| **Smoking habits, n (%)** | |
| Non-smoker | |
| Smoker | |
| Ex-smoker | |
| Total | |
| *If smoker/ex-smoker* | |
| **Smoking duration (years)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |
| **Number of cigarettes/day** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |

**Table 3 –** Chilbearing potential / Pregnancy test – ITT population

| | **Total (n=xx)** | | |
|---|---|---|---|
| | **Screening visit** | **Baseline** | **End of study treatmenttreatment** |
| *If female* | | | |
| **Childbearing potential and contraception, n (%)** | | | |
| Childbearing potential without contraceptive protection | | | |
| Childbearing potential with contraceptive protection | | | |
| xxxxx | | | |
| Xxxxx | | | |
| Xxxxx | | | |
| Surgically sterilized | | | |
| Postmenopausal | | | |
| Naturally sterile | | | |
| Abstinence/partner surgically sterile | | | |
| Total | | | |
| *If female patient is of childbearing* | | | |
| **Pregnancy test performed, n (%)** | | | |
| Yes | | | |
| No | | | |
| Total | | | |
| **Result of the pregnancy test, n (%)** | | | |
| Positive | | | |
| Negative | | | |
| Total | | | |
| *If male* | | | |
| **Use of the appropriate contraception protection, n (%)** | | | |
| Does not use contraceptive | | | |
| Uses contraceptive protection | | | |
| Surgically sterilized | | | |
| Naturally sterile | | | |
| Abstinence/partner surgically | | | |
| Total | | | |

**Table 4 –** Medical history: NSCLC Diagnosis – ITT population

| | **Total (n=xx)** |
|---|---|
| **Duration of disease (years)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |
| **Diagnosis technique, n (%)** | |
| Histology - Bronchoscopy | |
| Histology - Other | |
| Cytology - Sample FNA (Fine Needle Aspirate) | |
| Cytology - Sputum | |
| Cytology - Pleural effusion | |
| Cytology - Other | |
| Total | |
| **Patology results, n (%)** | |
| Adenocarcinoma | |
| Bronchoalveolar carcinoma | |
| Large cell carcinoma | |
| Squamous cells carcinoma | |
| Mixed cell type | |
| Other | |
| **TNM classification: T, n (%)** | |
| X | |
| 0 | |
| is | |
| 1a | |
| 1b | |
| 2 | |
| 3 | |
| 4 | |
| Total | |
| **TNM classification:N, n (%)** | |
| X | |
| 0 | |
| 1 | |
| 2a | |
| 2b | |
| 3 | |
| Total | |
| **TNM classification:M, n (%)** | |
| X | |
| 0 | |
| 1a | |
| 1b | |
| Total | |

**Table 4 (Cont.)** - Medical history: NSCLC Diagnosis – ITT population

| | **Total (n=xx)** |
|---|---|
| **TNM classification, n (%)** | |
| Occult carcinama | |
| Stage 0 | |
| Stage IA | |
| Stage IB | |
| Stage IIA | |
| Stage IIB | |
| Stage IIIA | |
| Stage IIIB | |
| Stage IV | |
| Total | |
| **Metastatic disease, n (%)** | |
| Adrenal glands | |
| Liver | |
| Brain | |
| Bone | |
| Other | |

**Table 5 –** Medical history: Co-mordidities – ITT population

| | **Total (n=xx)** |
|---|---|
| **Any co-morbidity, n (%)** | |
| Yes | |
| No | |
| Total | |
| *If yes:* | |
| **Grade, n (%)[a)]** | |
| Grade 1 | |
| Grade 2 | |
| Grade 3 | |
| Grade 4 | |
| Grade 5 | |
| Total | |
| **Severity, n (%)[a)]** | |
| Mild | |
| Moderate | |
| Severe | |
| Life threatning or disabling | |
| Death related | |

a) Percentage calculated within the total number of co-morbidities reported by ITT population (n=xxx).

**Table 6 –** Eastern cooperative oncology group performance status – ITT population

| | **Total (n=xx)** | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **ECOG result, n (%)** | | | | | |
| 0 | | | | | |
| 1 | | | | | |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |
| 5 | | | | | |
| Total | | | | | |
| **ECOG result** | | | | | |
| N | | | | | |
| Mean | | | | | |
| Median | | | | | |
| Standard Deviation | | | | | |
| Minimum | | | | | |
| Maximum | | | | | |

ECOG: Eastern Cooperative Oncology Group.

**Table 7 –** Concomitant medication – ITT population

| | **Total (n=xx)** |
|---|---|
| **Concomitant medication, n(%)** | |
| Yes | |
| No | |
| Total | |

**Table 8 –** Tumour assessment – ITT population

| | **Total (n=xx)** | | | |
|---|---|---|---|---|
| | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **Exam performed, n (%)** | | | | |
| CXR | | | | |
| Chest and upper abdomen CT Scan | | | | |
| Isotope Bone Scan | | | | |
| Brain CT Scan | | | | |
| Brain MRI | | | | |
| **CXR - result, n (%)** | | | | |
| Normal | | | | |
| Abnormal, clinically irrelevant | | | | |
| Abnormal, clinically relevant | | | | |
| Total | | | | |
| **Chest and upper abdomen CT Scan result, n (%)** | | | | |
| Normal | | | | |
| Abnormal, clinically irrelevant | | | | |
| Abnormal, clinically relevant | | | | |
| Total | | | | |
| **Chest and upper abdomen MRI result, n (%)** | | | | |
| Normal | | | | |
| Abnormal, clinically irrelevant | | | | |
| Abnormal, clinically relevant | | | | |
| Total | | | | |
| **Isotope Bone Scan - result, n (%)** | | | | |
| Normal | | | | |
| Abnormal, clinically irrelevant | | | | |
| Abnormal, clinically relevant | | | | |
| Total | | | | |
| **Brain CT Scan - result, n (%)** | | | | |
| Normal | | | | |
| Abnormal, clinically irrelevant | | | | |
| Abnormal, clinically relevant | | | | |
| Total | | | | |
| **Brain MRI - result, n (%)** | | | | |
| Normal | | | | |
| Abnormal, clinically irrelevant | | | | |
| Abnormal, clinically relevant | | | | |
| Total | | | | |

**Table 9 –** Clinical response: RECIST criteria – ITT population

| | **Total (n=xx)** | | |
|---|---|---|---|
| | | **Visit xx** | **End of study treatment** |
| **Target lesion** | | | |
| **Response, n(%)** | | | |
| Complete response | | | |
| Partial response | | | |
| Stable disease | | | |
| Progressive disease | | | |
| Not all evaluable | | | |
| Any | | | |
| Total | | | |
| **Assessment exam, n (%)** | | | |
| CT Scan | | | |
| MRI | | | |
| Spiral CT Scan | | | |
| Total | | | |
| **Lesion location, n (%)** | | | |
| Brain | | | |
| Liver | | | |
| Lymph nodes | | | |
| Bones | | | |
| Skin | | | |
| Peritoneum | | | |
| Lung | | | |
| Other | | | |
| **Measurable lesion longest diameter (mm)** | | | |
| N | | | |
| Mean | | | |
| Median | | | |
| Standard Deviation | | | |
| Minimum | | | |
| Maximum | | | |
| | | | |
| **Non-target lesion** | | | |
| **Response, n(%)** | | | |
| Complete response | | | |
| Non-CR | | | |
| Non-PD | | | |
| Progressive disease | | | |
| Not all evaluable | | | |
| Any | | | |
| Total | | | |
| **Assessment exam, n (%)** | | | |
| CT Scan | | | |
| MRI | | | |
| Spiral CT Scan | | | |
| Total | | | |
| **Lesion location, n (%)** | | | |
| xxxx | | | |
| xxxx | | | |
| xxxx | | | |
| **Lesion assessment, n (%)** | | | |
| Present | | | |
| Absent | | | |
| Unequivocal progression | | | |
| Total | | | |

**Tabel 9 (Cont.)** - Clinical response: RECIST criteria – ITT population

| | **Total (n=xx)** | | |
|---|---|---|---|
| | | **Visit xx** | **End of study treatment** |
| **New lesions, n (%)** | | | |
| Yes | | | |
| No | | | |
| Total | | | |
| **Overall response, n(%)** | | | |
| Complete response | | | |
| Partial response | | | |
| Stable disease | | | |
| Progressive disease | | | |
| Inevaluable | | | |
| Total | | | |

**Table 10 –** Best overall response: RECIST criteria – ITT population

| | **Total (n=xx)** |
|---|---|
| **Best overall response, n(%)** | |
| Complete response | |
| Partial response | |
| Stable disease | |
| Progressive disease | |
| Inevaluable | |
| Total | |
| **Objective response rate[a], n (%), 95% CI** | |

a) Objective response rate: patients with complete or partial response.
95% CI: 95% confidence interval.

**Table 11 –** Best overall response: RECIST criteria – PP population

| | **Total (n=xx)** |
|---|---|
| **Best overall response, n(%)** | |
| Complete response | |
| Partial response | |
| Stable disease | |
| Progressive disease | |
| Inevaluable | |
| Total | |
| **Objective response rate[a], n (%), 95% CI** | |

a) Objective response rate: patients with complete or partial response.
95% CI: 95% confidence interval.

**Table 12 –** Progression free survival – ITT population

| | Statistics | $CI_{95\%}$ |
|---|---|---|
| **PFS (weeks)** | | |
| N | | |
| Censored | | |
| Events (disease progression or death) | | |
| Mean | | |
| Median | | |
| Percentile 25% | | |
| Percentile 75% | | |
| Minimum | | |
| Maximum | | |

PFS: Progression free survival.
$CI_{95\%}$: 95% confidence interval.

**Table 13 –** Progression free survival – PP population

| | Statistics | $CI_{95\%}$ |
|---|---|---|
| **PFS (weeks)** | | |
| N | | |
| Censored | | |
| Events (disease progression or death) | | |
| Mean | | |
| Median | | |
| Percentile 25% | | |
| Percentile 75% | | |
| Minimum | | |
| Maximum | | |

PFS: Progression free survival.
$CI_{95\%}$: 95% confidence interval.

**Table 14 –** Overall survival – ITT population

| | **Statistics** | **$CI_{95\%}$** |
|---|---|---|
| **Overall survival (weeks)** | | |
| N | | |
| Censored | | |
| Events (death) | | |
| Mean | | |
| Median | | |
| Percentile 25% | | |
| Percentile 75% | | |
| Minimum | | |
| Maximum | | |

$CI_{95\%}$: 95% confidence interval.

**Table 15 –** Overall survival – PP population

| | **Statistics** | **$CI_{95\%}$** |
|---|---|---|
| **Overall survival (weeks)** | | |
| N | | |
| Censored | | |
| Events (death) | | |
| Mean | | |
| Median | | |
| Percentile 25% | | |
| Percentile 75% | | |
| Minimum | | |
| Maximum | | |

$CI_{95\%}$: 95% confidence interval.

**Table 16 –** Epidermal growth factor receptor – All patients

| | **Total (n=xx)** |
|---|---|
| **EGFR test performed, n(%)** | |
| Yes | |
| No | |
| Total | |
| **EGFR positive result, n (%), 95% CI** | |
| Positive | |
| Negative | |
| Total | |
| **Exon 19 and/or exon 21 mutations, n (%)** | |
| Exon 19 | |
| Exon 21 | |

Positive result: patients with Exon 19 and/or exon 21 mutations.

**Table 17 –** Epidermal growth factor receptor

| | **Total (n=xx)** |
|---|---|
| **Exon 19 and/or exon 21 mutations, n (%)** | |
| **ITT Population** | |
| Exon 19 | |
| Exon 21 | |
| **PP Population** | |
| Exon 19 | |
| Exon 21 | |

Positive result: patients with Exon 19 and/or exon 21 mutations.

**Table 18 –** Response duration– ITT population

| | **Statistics** | **$CI_{95\%}$** |
|---|---|---|
| **Response duration (weeks)** | | |
| N | | |
| Censored | | |
| Events (death) | | |
| Mean | | |
| Median | | |
| Percentile 25% | | |
| Percentile 75% | | |
| Minimum | | |
| Maximum | | |

$CI_{95\%}$: 95% confidence interval.

**Table 19 –** Response duration– PP population

| | Statistics | $CI_{95\%}$ |
|---|---|---|
| **Response duration (weeks)** | | |
| N | | |
| Censored | | |
| Events (death) | | |
| Mean | | |
| Median | | |
| Percentile 25% | | |
| Percentile 75% | | |
| Minimum | | |
| Maximum | | |

$CI_{95\%}$: 95% confidence interval.

**Table 20 –** Progression free survival by exon 19 and 21– ITT population

| | Exon 19 | | Exon 21 | |
|---|---|---|---|---|
| | **Statistics** | **$CI_{95\%}$** | **Statistics** | **$CI_{95\%}$** |
| **PFS (weeks)** | | | | |
| N | | | | |
| Censored | | | | |
| Events (disease progression or | | | | |
| Mean | | | | |
| Median | | | | |
| Percentile 25% | | | | |
| Percentile 75% | | | | |
| Minimum | | | | |
| Maximum | | | | |

PFS: Progression free survival.
$CI_{95\%}$: 95% confidence interval.

**Table 21 –** Progression free survival by exon 19 and 21– PP population

| | Exon 19 | | Exon 21 | |
|---|---|---|---|---|
| | **Statistics** | **$CI_{95\%}$** | **Statistics** | **$CI_{95\%}$** |
| **PFS (weeks)** | | | | |
| N | | | | |
| Censored | | | | |
| Events (disease progression or | | | | |
| Mean | | | | |
| Median | | | | |
| Percentile 25% | | | | |
| Percentile 75% | | | | |
| Minimum | | | | |
| Maximum | | | | |

PFS: Progression free survival.
$CI_{95\%}$: 95% confidence interval.

**Table 22 –** Drug dispensing and accountability – Safety population

| | **Total (n=xx)** |
|---|---|
| **Starting dose of study drug, n (%)** | |
| 150 mg | |
| 100 mg | |
| 50 mg | |
| Total | |
| **Reduction in starting dose, n (%)** | |
| Yes | |
| No | |
| Total | |
| **Dose per day (mg)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |
| **Cumulative dose (mg)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |
| **Duration of study drug dispensability (weeks)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |
| **Study drug dispensed (tablets)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |
| **Study drug used (tablets)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |
| **Study drug unused (tablets)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |

**Table 22 (Cont.)** – Drug dispensing and accountability – Safety population

| | **Total (n=xx)** |
|---|---|
| **Study drug missing (tablets)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |
| **Drug compliance (%)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |
| **Patient compliant, n (%)** | |
| Yes | |
| No | |
| Total | |

**Table 23 –** Physical examination – Safety population

| | Total (n=xx) | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **Physical examination rerformed, n (%)** | | | | | |
| Yes | | | | | |
| No | | | | | |
| Total | | | | | |
| **Skin examination, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal | | | | | |
| Total | | | | | |
| **Nails examination, n(%)** | | | | | |
| Normal | | | | | |
| Abnormal | | | | | |
| Total | | | | | |
| **Thorax examination, n(%)** | | | | | |
| Normal | | | | | |
| Abnormal | | | | | |
| Total | | | | | |
| **Abdomen examination, n(%)** | | | | | |
| Normal | | | | | |
| Abnormal | | | | | |
| Total | | | | | |
| **Extremities examination, n(%)** | | | | | |
| Normal | | | | | |
| Abnormal | | | | | |
| Total | | | | | |
| **Head examination, n(%)** | | | | | |
| Normal | | | | | |
| Abnormal | | | | | |
| Total | | | | | |
| **Genital examination, n(%)** | | | | | |
| Normal | | | | | |
| Abnormal | | | | | |
| Total | | | | | |
| **Neurologic examination, n(%)** | | | | | |
| Normal | | | | | |
| Abnormal | | | | | |
| Total | | | | | |
| **Temperature examination, n(%)** | | | | | |
| Normal | | | | | |
| Abnormal | | | | | |
| Total | | | | | |
| **Other physical examination, n(%)** | | | | | |
| Yes | | | | | |
| No | | | | | |
| Total | | | | | |

**Table 24 –** Electrocardiogram – Safety population

| | **Total (n=xx)** | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **ECG performed, n (%)** | | | | | |
| Yes | | | | | |
| No | | | | | |
| Total | | | | | |
| **ECG result, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |

ECG: Electrocardiogram.

**Table 25 –** Hematology – Safety population

| | **Total (n=xx)** | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **Hemoglobin, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |
| **Leucocytes, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |

**Table 25 (Cont.)** – Hematology – Safety population

| | **Total (n=xx)** | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **Neutrophils, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |
| **Platelets, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |

**Table 26 –** Coagulation – Safety population

| | **Total (n=xx)** | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **Prothrombin time, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |
| **APTT, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |
| **INR, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |

**Table 26 (Cont.)** – Coagulation – Safety population

| | **Total (n=xx)** | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **INR, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |

**Table 27 –** Biochemistry – Safety population

| | **Total (n=xx)** | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **Urea, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |
| **Glucose, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |

**Table 27 (Cont.)** – Biochemistry – Safety population

| | **Total (n=xx)** | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **AST, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |
| **ALT, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |

**Table 27 (Cont.)** – Biochemistry – Safety population

| | Total (n=xx) | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **Creatinine clearance, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |
| **Serum creatinine, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |

**Table 27 (Cont.)** – Biochemistry – Safety population

| | Total (n=xx) | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **Calcium, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |
| **Sodium, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |

**Table 27 (Cont.)** – Biochemistry – Safety population

| | Total (n=xx) | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **Potassium, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |
| **Chloride, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |

**Table 27 (Cont.)** – Biochemistry – Safety population

| | Total (n=xx) | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **LDH, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |
| **Alkaline phosphatase, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |

**Table 27 (Cont.)** – Biochemistry – Safety population

| | **Total (n=xx)** | | | | |
|---|---|---|---|---|---|
| | **Screening** | **Baseline** | **Visit xx** | **End of study treatment** | **End of study** |
| **Total bilirubin, n (%)** | | | | | |
| Normal | | | | | |
| Abnormal, clinically irrelevant | | | | | |
| Abnormal, clinically relevant | | | | | |
| Total | | | | | |
| *Baseline versus current visit* | | | | | |
| Normal - Normal | - | - | - | - | |
| Normal - Abnormal, clinically irrelevant | - | - | - | - | |
| Normal - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Normal | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically irrelevant | - | - | - | - | |
| Abnormal, clinically irrelevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Normal | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically relevant | - | - | - | - | |
| Abnormal, clinically relevant - Abnormal, clinically irrelevant | - | - | - | - | |

**Table 28 –** Adverse events and serious adverse events – Safety population

| | **Total (n=xx)** |
|---|---|
| **Patients with at least one adverse event, n (%)[a)]** | |
| No | |
| Yes | |
| Total | |
| **Patients with at least one serious adverse event, n (%)[a)]** | |
| Yes | |
| No | |
| Total | |
| **Patients with at least one adverse event of special interest, n (%)[a)]** | |
| Stevens-Johnson Syndrom | |
| Interstitial Lung Disease | |
| **Grade of adverse events, n (%)[b)]** | |
| Grade 1 | |
| Grade 2 | |
| Grade 3 | |
| Grade 4 | |
| Grade 5 | |
| Total | |
| **Severity of adverse events, n (%)[b)]** | |
| Mild | |
| Moderate | |
| Severe | |
| Life threatning or disabling | |
| Death related | |
| Total | |
| **Relationship of study drug, n (%)[b)]** | |
| Unrelated | |
| Remote relation | |
| Possible relation | |
| Probable relation | |
| Total | |
| **Action taken for adverse event, n (%)[b)]** | |
| Dose increased | |
| Dose not changed | |
| Dose reduced | |
| Drug interrupted | |
| Drug withdrawn | |
| Not applicable | |
| Unknown | |
| **Serious adverse events, n (%)[b)]** | |
| Yes | |
| No | |
| **Outcome, n (%)[b)]** | |
| Not recovered / Not resolve | |
| Recovering / Resolving | |
| Recovered / Resolved | |
| Recovered / Resolved with sequelae | |
| Fatal | |
| Unknown | |

a) Percentage calculated within the total number of patients of safety population (n=xx).
b) Percentage calculated within the total number of adverse events reported by safety population (n=xxx).

**Table 29 –** Incidence of adverse events – Safety population

| | **Total (n=xx)** |
|---|---|
| **Incidence of adverse events, n (%)** | |
| **Body system 1** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |
| **Body system 2** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |

a) Percentage calculated for total of patients of patients of the safety population (n=xx).

**Table 30 –** Incidence of serious adverse events – Safety population

| | **Total (n=xx)** |
|---|---|
| **Incidence of serious adverse events, n (%)** | |
| **Body system 1** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |
| **Body system 2** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |

a) Percentage calculated for total of patients of patients of the safety population (n=xx).

**Table 31 –** Incidence of adverse events with remote, possible or probable relationship with study drug – Safety population

| | **Total (n=xx)** |
|---|---|
| **Incidence of adverse events with remote, possible or probable relationship with study drug, n (%)** | |
| **Body system 1** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |
| **Body system 2** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |

a) Percentage calculated for total of patients of patients of the safety population (n=xx).

**Table 32 –** Incidence of serious adverse events with remote, possible or probable relationship with study drug – Safety population

| | **Total (n=xx)** |
|---|---|
| **Incidence of serious adverse events with remote, possible or probable relationship with study drug, n (%)** | |
| **Body system 1** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |
| **Body system 2** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |

a) Percentage calculated for total of patients of patients of the safety population (n=xx).

**Table 33 –** Adverse events – Safety population

| | **Total (n=xx)** |
|---|---|
| **Adverse events, n (%)** | |
| **Body system 1** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |
| **Body system 2** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |

Percentage calculated within the total number of adverse events reported by safety population (n=xxxx).

**Table 34 –** Serious adverse events – Safety population

| | **Total (n=xx)** |
|---|---|
| **Serious adverse events, n (%)** | |
| **Body system 1** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |
| **Body system 2** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |

Percentage calculated within the total number of serious adverse events reported by safety population (n=xxxx).

**Table 35 –** Adverse events with remote, possible or probable relationship with study drug – Safety population

| | **Total (n=xx)** |
|---|---|
| **Adverse events with remote, possible or probable relationship with study drug, n (%)** | |
| **Body system 1** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |
| **Body system 2** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |

Percentage calculated within the total number of adverse events with remote, possible or probable relationship with study drug reported by safety population (n=xxxx).

**Table 36 –** Serious adverse events with remote, possible or probable relationship with study drug – Safety population

| | **Total (n=xx)** |
|---|---|
| **Serious adverse events with remote, possible or probable relationship with study drug, n (%)** | |
| **Body system 1** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |
| **Body system 2** | |
| Xxxxx | |
| Xxxxx | |
| Xxxxx | |

Percentage calculated within the total number of serious adverse events with remote, possible or probable relationship with study drug reported by safety population (n=xxxx).

**Table 37 –** Adverse envents of special interest: Interstitial lung disease – Safety population

| | **Total (n=xx)** |
|---|---|
| **Time to first onset, n (%)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |
| **Total number of episodes, n (%)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |

**Table 38 –** Adverse envents of special interest: Stevens-Johnson syndrome – Safety population

| | **Total (n=xx)** |
|---|---|
| **Time to first onset, n (%)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |
| **Total number of episodes, n (%)** | |
| N | |
| Mean | |
| Median | |
| Standard Deviation | |
| Minimum | |
| Maximum | |

**Table 39 –** Subsequent therapy for NSCLC – Safety population

| | **Total (n=xx)** |
|---|---|
| | **Visit XX** |
| **Subsequent therapy, n (%)** | |
| Yes | |
| No | |
| Total | |
| **Therapeutic line, n (%)** | |
| Second | |
| Third / Fourth | |
| Paliative Care | |
| Total | |
| **Treatment** | |
| Xxxx | |
| Xxxx | |
| Xxxx | |
| Xxxx | |
| Xxxx | |
| Xxxx | |

# Appendix 7: Listings

**Listing 1** – Co-morbidities – ITT population

| Center | Patient | Co-morbidity | Grade | Severity | Start year |
|---|---|---|---|---|---|

**Listing 2** – Abnormal findings in ECOG results – ITT population

| Center | Patient | Date | Location | Result | Description |
|---|---|---|---|---|---|

**Listing 3** – Concomitant medication – ITT population

| Center | Patient | Treatment name | Indication | Dose | Unit | Route | Frequency | First taken | Ongoing | Last taken |
|---|---|---|---|---|---|---|---|---|---|---|

**Listing 4** – Adverse events – Safety population

| Center | Patient | Adverse event | Grade | Severity | Relationship | Outcome | Action taken | Seriousness | Date started | Date ended | Duration of AE | AE related Concomitant Medication |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | |