



ETOP 7-14 NICHE

Afatinib in pretreated patients with advanced NSCLC harbouring *HER2* exon 20 mutations

NICHE = afatinib in NSCLC with HER2 mutation

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In collaboration with Boehringer Ingelheim Pharma GmbH & Co. KG

Protocol Signature Page

Afatinib in pretreated patients with advanced NSCLC harbouring *HER2* exon 20 mutations

ETOP 7-14 NICHE

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Principal Investigator Protocol Signature Page

Afatinib in pretreated patients with advanced NSCLC harbouring *HER2* exon 20 mutations

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I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with GCP, and will apply due diligence to avoid protocol deviations. I will provide copies of the protocol and all drug information relating to pre-clinical and prior clinical experience furnished to me by ETOP, to all physicians responsible to me who participate in this trial. I will discuss this material with them to assure that they are fully informed regarding the drug and the conduct of the trial. I agree to keep accurate records on all patient information including patient's informed consent statement, drug shipment and return forms, and all other information collected during the trial for a minimum period of 15 years.

Name of Principal Investigator: _____

Institution's name and place: _____

Signature

Date

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1. Protocol Summary

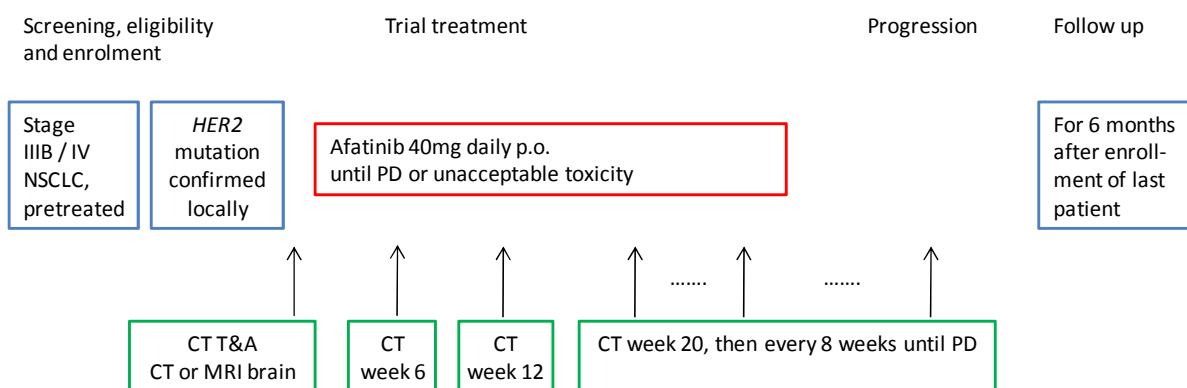
ETOP 7-14 NICHE – Afatinib in pretreated patients with advanced NSCLC harbouring *HER2* exon 20 mutations

Sponsor: European Thoracic Oncology Platform (ETOP)

Pharma Partner: Boehringer Ingelheim Pharma GmbH & Co. KG

Population: Advanced stage NSCLC, harbouring *HER2* exon 20 mutations.

Design: Phase II single-arm multicenter trial



Sample size: 22 patients

Rationale:

Human cancers usually evolve through multistep processes. These processes are driven by the accumulation of abundant genetic and epigenetic abnormalities. However, some lung cancers depend on a single activated oncogene by somatic mutation, termed “driver oncogenic mutations”, for their proliferation and survival. *EGFR* mutations and *ALK* rearrangement are typical examples of such driver oncogenic mutations found in lung adenocarcinomas. *EGFR*-tyrosine kinase inhibitors (TKIs) like erlotinib, gefitinib or afatinib or *ALK*-TKIs, like crizotinib, ceritinib or alectinib, significantly improved treatment outcomes compared with conventional cytotoxic chemotherapy in patients with lung cancers harboring *EGFR* mutations or *ALK*-rearrangement, respectively.

Human epidermal growth factor 2 receptor (HER2, erbB-2/neu) is a member of the erbB receptor tyrosine kinase family. The *ERBB2* gene which encodes for HER2 is a major proliferative driver that activates downstream signaling through PI3K-AKT and MEK-ERK pathways. No ligand has been described for this receptor, which is activated by homo-dimerization or hetero-dimerization with other members of the erbB family.

HER2 mutations consist of in-frame insertions in exon 20, leading to constitutive activation of the receptor and downstream AKT and MEK pathways. *HER2* mutations respond to the genetic « driver » and preclinical models have proved the concept of transforming property

of such a genetic alteration. Inducible expression of a *HER2* mutant (*HER2*^{YVMA}) in lung epithelium of mice results in the emergence of invasive adenosquamous carcinomas, with tumour maintenance requiring the continuous expression of the driver, as observed with EGFR-driven cancer.

HER2 protein overexpression and gene amplification are present in 6–35% and in 10–20%, respectively, of NSCLC. *HER2* mutations were identified in about 2–4% of NSCLC. In the selected population of EGFR/KRAS/ALK negative patients, *HER2* mutations can reach up to 6%. This mutation is predominantly observed in females, non-smokers and adenocarcinoma subtype, similar to *EGFR* mutated NSCLC. *HER2* mutations have never been observed concomitantly with *EGFR* mutations or ALK rearrangement.

Among reported lung cancer biomarkers, *HER2* as a target remains poorly described. *HER2* overexpression or gene amplification is widely known to be associated with sensitivity to *HER2*-targeting drugs (trastuzumab, lapatinib, pertuzumab and T-DM1) in breast cancer. Involvement of *HER2* in lung carcinogenesis has been known for many years, but clinical research was slowed down when the first clinical trials with trastuzumab were negative. Indeed, the addition of trastuzumab to gemcitabine-cisplatin or to docetaxel failed to show any survival benefit in *HER2* Immuno-Histo-Chemistry-positive (IHC) lung cancer patients. However, *HER2* mutations may be more relevant in lung carcinogenesis than *HER2* amplification or overexpression.

Afatinib (BIBW2992) is a small molecule, selective and irreversible erbB family blocker. In preclinical models it effectively inhibits EGFR, *HER2* and *HER4* phosphorylation resulting in tumour growth inhibition and regression of established subcutaneous tumours derived from four human cell-lines known to co-express ErbB receptors.

HER2 mutations are identified in about 2% of non-small-cell lung cancers (NSCLC) and appear to be critical for lung carcinogenesis. There are very few data available that describe the clinical course of *HER2* mutated NSCLC patients. Mazieres and colleagues recently retrospectively identified 65 NSCLC patients diagnosed with a *HER2* in-frame insertion in exon 20. The *HER2* mutation was almost an exclusive driver, except one single case with a concomitant *KRAS* mutation. All tumours were adenocarcinomas and 50% were stage IV at diagnosis. For these latter cases, 22 anti-*HER2* treatments were administered after conventional chemotherapy in 16 patients. Subsequently, four progressive disease, seven disease stabilizations and eleven partial responses (overall response rate ORR 50%; disease control rate DCR 82%) were observed. Specifically, they observed a DCR of 93% for trastuzumab-based therapies (n = 15), 100 % DCR for afatinib (n = 3), but no response to other *HER2*-targeted drugs (n = 3). Progression free survival for patients with *HER2*-therapies was 5.1 months. Median survival was of 89.6 and 22.9 months for early stage and stage IV patients, respectively. This study, the largest to date dedicated to *HER2*-mutated NSCLC, reinforced the importance of screening for *HER2*-mutations in lung adenocarcinomas, and suggested the potential efficacy of *HER2*-targeted drugs in this population. Additionally, single case reports suggest that *HER2* mutations may be predictive for *HER2* targeting therapies in lung cancer. Some ongoing clinical trials are enrolling patients with *HER2* mutated NSCLC, mixed together with *HER2* amplified or *EGFR*

mutated NSCLC cases. Large biomarker screening programs such as the French National Program or the US Lung Cancer Mutation Consortium (LCMC) thus propose testing for *HER2* mutations.

Afatinib presents a manageable toxicity profile and potentially offers a significant activity in terms of disease control and long term outcome. Therefore this treatment option offers a good benefit to risk ratio in patients with *HER2*-mutated advanced NSCLC.

Objectives and endpoints:

The primary objective is to evaluate the ability of afatinib to control disease in pretreated patients with advanced NSCLC harbouring *HER2* exon 20 mutations.

Primary endpoint: disease control at 12 weeks

Secondary endpoints:

- Progression-free survival by RECIST 1.1
- Objective response determined by RECIST 1.1
- Overall survival
- Adverse events graded according to CTCAE V4.0

Most important eligibility criteria (see protocol section 7 for complete list):

Inclusion criteria at enrolment:

- Histologically or cytologically confirmed, non-predominant squamous subtype, stage IIIB (non amenable to curative-intent multimodal treatment) or IV NSCLC, according to 7th TNM classification
- Tumour is platinum-refractory
- Measurable or evaluable disease (according to RECIST 1.1 criteria)
- Locally documented *HER2* mutation
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2
- Life expectancy ≥ 3 months
- Adequate haematological, renal and hepatic function
- Effective contraception, no pregnancy

Exclusion criteria at enrolment:

- Mixed small-cell and non-small-cell histologic features
- Uncontrolled lepto-meningeal metastatic disease
- Previous treatment with *HER2* targeted antibody or tyrosine kinase inhibitor
- Any previous (in the past 3 years) or concomitant malignancy EXCEPT adequately treated basal or squamous cell carcinoma of the skin, *in situ* carcinoma of the cervix or bladder, *in situ* ductal carcinoma of the breast
- History or presence of clinically relevant cardiovascular abnormalities
- Other serious diseases or clinical conditions, including but not limited to uncontrolled active infection and any other serious underlying medical processes that could affect the patient's capacity to participate in the trial
- Interstitial lung disease or pulmonary fibrosis
- Any concurrent systemic anticancer therapy

Treatment:

Afatinib 40 mg p.o./day until tumour progression or lack of tolerability

Statistical considerations:

Simon's two stage phase II design is adopted. A Disease Control Rate (DCR) of 50% is considered as unacceptable, targeting a DCR of 75%. Hence the null hypothesis under consideration is that the $DCR \leq 50\%$ versus the alternative that $DCR \geq 75\%$. For a one-sided type I error of 10% and power of 80%, a total of 22 patients are needed, with 9 patients in the first stage. If in the first stage, 6 out of the 9 patients achieve Disease Control, then the trial will proceed to the second stage and recruit an additional 13 patients for a total of 22 patients. If at least 14 out of the 22 patients achieve Disease Control, then this finding will indicate that it would be reasonable to proceed to a Phase III trial.

Total trial duration: 40 months from enrolment of the first patient, including 6 months of follow-up from enrolment of the last patient.

2. Trial schedule

(refer to section 15 for details)

	Screening and eligibility within 28 days prior to enrolment	Afatinib treatment visits ¹³	End of treatment visit (within 30 days after treat. stop)	Follow-up before progression ¹⁴	Follow-up after progression ¹⁴
Written informed consent ¹	X				
Medical history	X				
Physical exam ² , PS, weight	X	X	X ³		
Local HER2-testing ¹⁵	X				
Haematology (WBC, haemoglobin, platelets, neutrophils)	X ⁴	X	X		
Chemistry: Na, K, calcium, albumin, magnesium	X ⁴	X ⁵	X		
Renal function: serum creatinine, calculated creatinine clearance	X	X	X		
Hepatic function: ALT, AST, bilirubin, GGT	X	X	X		
Electrocardiogram	X				
Pregnancy test if applicable ⁶	X		X		
CT thorax and upper abdomen ⁷	X	X	X ⁸	X ⁹	
Brain MRI or CT	X				
FFPE block (or 5-10 slides) from (primary or metastatic) biopsy for retrospective central HER2-testing	X ¹⁰				
Adverse events ¹¹	X	X ¹²	X	X	X
Record concomitant medication ¹¹		X	X	X	X
Afatinib 40mg p.o. daily until PD		X ¹²			
Survival status					X

- 1 – Any time before any trial-specific intervention
- 2 – Physical exam according to local standards, including blood pressure
- 3 – Blood pressure does not need to be reported at end of treatment visit.
- 4 – If haematology and/or chemistry were done more than 7 days prior to first dose, they need to be repeated before starting afatinib treatment.
- 5 – Will be repeated if clinically indicated according to local standards
- 6 – Women of childbearing potential (< 1 year without menstruation or < 2 years without menstruation following chemotherapy) must have a negative serum or urine pregnancy test before enrolment to the trial; the test has to be repeated within 7 days before starting afatinib treatment. Pregnancy tests should be repeated within 30 days after afatinib treatment stop. Any pregnancy occurring during treatment or within 6 months after treatment stop must be reported including its outcome.
- 7 – All patients must have a CT thorax and upper abdomen at baseline during screening, 6 and 12 weeks after first dose of trial treatment and then every 8 weeks (weeks 20, 28, 36 etc) until progression.
- 8 – CT to be repeated if not done within 6 weeks prior to end of treatment visit.
- 9 – In case of treatment stop for reason other than progressive disease, CT needs to be repeated every 8 weeks until progression.
- 10 – Tissue collection for central histological subtype pathology review; mutation for HER2; potential future translational research.
- 11 – Symptoms present at baseline will be recorded on the adverse event form as well from date of informed consent. In follow-up, AEs and concomitant medication will be recorded until 90 days after stop of trial treatment.
- 12 – During the first cycle of 3 weeks, regular contact with patient to monitor adverse events, especially diarrhea (phone contact allowed).
- 13 – Visits will be planned at start of treatment (week 0), week 3, 6, 9, 12 and then every 4 weeks. Patient diary should be checked and tablets returned should be counted.
- 14 – Follow-up visits after treatment stop, before progression: every 8 weeks, coinciding with imaging visits; after progression, record survival status every 3 months until 6 months after inclusion of the last patient.
- 15 – Can be from mutation test done prior to screening phase.

3. List of abbreviations

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AESI	Adverse event of special interest
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area Under the Curve
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DILI	Drug-induced liver injury
DSUR	Development Safety Update Report
ECOG	Eastern Cooperative Oncology Groupe
eCRF	Electronic Case Report Form
EEA	European Economic Area
EGFR	epidermal growth factor receptor
EOT	End of Treatment
ERB	Ethical Review Board
FFPE	Formalin fixed, paraffin embedded
FISH	Fluorescence in situ Hybridization
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
HER2/ ERBB2	Human Epidermal growth factor 2 Receptor
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IC	Informed Consent
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Institutional Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
KRAS	Kirsten Rat Sarcoma
LCMC	Lung Cancer Mutation Consortium
MEK-ERK	Mitogen-Activated Protein Kinase/Extracellular-Signal Regulated Kinase

MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
P-GP	Permeability Glycoprotein
PIK-AKT	Phosphatidylinositol 3-Kinases and Protein Kinase B
PK	Pharmacokinetics
PR	Partial Response
RDE	Remote Data Entry
RECIST	Response Evaluation Criteria In Solid Tumours
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCLC	Small cell lung carcinoma
SD	Stable Disease
SPF	Sun Protection Factor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TKI	Tyrosine Kinase Inhibitor
TNM	Tumour, Nodes, Metastasis
ULN	Upper limit of normal lab value
WBC	White Blood Cells

4. Background and Rationale

4.1. Disease background

Primary lung cancer is the most common malignancy after non-melanocytic skin cancer with deaths from lung cancer exceeding those from any other type of malignancy worldwide [1]. While it has been the most important cause of cancer mortality in men since the 1960s, it has equalled breast cancer as a cause of mortality in women since the 1990s.

Lung cancer accounts for 12% of all incident cases of cancer. Non-small cell lung cancers (NSCLC) account for 80-85% of lung cancers, while small cell lung cancer (SCLC) has been decreasing in frequency in many countries over the last 2 decades [2].

Advanced stage NSCLC is traditionally treated by systemic palliative chemotherapy. Several distinct chemotherapy regimens have shown comparable efficacy with different toxicity profiles that are taken into account for treatment selection [3]. Fundamentally, chemotherapy efficacy seems to have reached a plateau. Since 1978, cisplatin has been the basis of chemotherapy treatment of NSCLC. However, in unselected patients, response rates are only 15-30% and median survival is 10-12 months, while the majority of patients suffer severe side effects with no therapeutic benefit. The treatment of cancer patients is characterized by great inter-individual variability in outcome and evidence indicates that response is determined in part by patient-specific alterations in the somatic cancer genome and changes in gene expression. The use of a platinum-based chemotherapy combination is the backbone of first-line treatment for epidermal growth factor (EGFR) or ALK (anaplastic lymphoma kinase)-wild-type advanced NSCLC patients. There is an unmet need for molecular predictive markers that could identify both patients most likely to benefit from platinum-based treatment and those resistant to treatment, thus optimizing chemotherapy approach in NSCLC. Since 1994, molecular research has centered on the identification of predictive biomarkers that can be successfully used to tailor treatment in these patients. To date, however, no genetic marker has been validated in a biomarker-directed randomised trial.

4.2. Targeted agents in non-small cell lung cancer

Human cancers usually evolve through multistep processes. These processes are driven by the accumulation of abundant genetic and epigenetic abnormalities. However, some lung cancers depend on a single activated oncogene by somatic mutation, termed “driver oncogenic mutations”, for their proliferation and survival. *EGFR* mutations and *ALK* rearrangement are typical examples of such driver oncogenic mutations found in lung adenocarcinomas. *EGFR*-tyrosine kinase inhibitors (TKIs) like erlotinib, gefitinib or afatinib or *ALK*-TKIs, like crizotinib, ceritinib or alectinib, significantly improved treatment outcomes compared with conventional cytotoxic chemotherapy in patients with lung cancers harboring *EGFR* mutations or *ALK*-rearrangement, respectively. Therefore, treatment strategies for lung cancers have dramatically changed from a “general and empiric” to a “personalized and evidence-based” approach according to the driver oncogenic mutation.

Several novel driver oncogenic mutations, which are candidates as novel targets, such as *HER2*, *BRAF*, *ROS1*, and *RET*, have been discovered. Some drugs have been shown to inhibit more than one of the quite homologous cancer-related human kinases. For example, crizotinib also achieves high response rates in anaplastic lymphoma kinase (ALK)-translocated and ROS1-translocated NSCLC patients.

4.3. HER2

Human epidermal growth factor 2 (HER2, erbB-2/neu) is a member of the erbB receptor tyrosine kinase family. The *ERBB2* gene which encodes for HER2 is a major proliferative driver that activates downstream signaling through PI3K-AKT and MEK-ERK pathways [4]. No ligand has been described for this receptor, which is activated by homo-dimerization or hetero-dimerization with other members of the erbB family.

HER2 mutations consist of in-frame insertions in exon 20, leading to constitutive activation of the receptor and downstream AKT and MEK pathways. *HER2*-mutations respond to the genetic « driver » and preclinical models have proved the concept of transforming property of such a genetic alteration [5]. Inducible expression of a *HER2* mutant (HER2^{YVMA}) in lung epithelium of mice results in the emergence of invasive adenosquamous carcinomas, with tumour maintenance requiring the continuous expression of the driver, as observed with EGFR-driven cancer.

HER2 protein overexpression and gene amplification are present in 6–35% and in 10-20%, respectively, of NSCLC. *HER2* mutations were identified in about 2-4% of NSCLC. In the selected population of EGFR/KRAS/ALK negative patients, *HER2* mutations can reach up to 6%. This mutation is predominantly observed in females, non-smokers and adenocarcinoma subtype, similar to *EGFR* mutated NSCLC. *HER2* mutations have never observed concomitantly with *EGFR* mutations or ALK rearrangement [6].

Among reported lung cancer biomarkers, *HER2* as a target remains poorly described. *HER2* overexpression or gene amplification is widely known to be associated with sensitivity to *HER2*-targeting drugs (trastuzumab, lapatinib, pertuzumab and T-DM1) in breast cancer [7]. Involvement of *HER2* in lung carcinogenesis has been known for many years, but clinical research was slowed down when the first clinical trials with trastuzumab were negative. Indeed, the addition of trastuzumab to gemcitabine-cisplatin or to docetaxel failed to show any survival benefit in *HER2* Immuno-Histo-Chemistry-positive (IHC) lung cancer patients [8]. However, *HER2* mutations may be more relevant in lung carcinogenesis than *HER2* amplification or overexpression.

Clinically relevant *HER2* mutations are clustered in exon 20 of the *HER2* gene and commonly include small exon 20 insertions (majority of patients), clustered or single amino acid substitutions all nested in the most proximal region of the exon, between codons 775 and 881. In the study of Arcila *et al*, the frequency of *HER2* mutations among lung adenocarcinoma patients was 26/1478 (approx. 2%). *HER2* insertions identified in this study included A775_G776insYVMA (80% of tumours), G776>VC, V777_G778insCG and P780_Y781insGSP and point mutations included L755S and G776C [9].

4.4. Afatinib

Afatinib (BIBW2992) is a small molecule, selective and irreversible erbB family blocker. In preclinical models it effectively inhibits EGFR, HER2 and HER4 phosphorylation resulting in tumour growth inhibition and regression of established subcutaneous tumours derived from four human cell-lines known to co-express ErbB receptors.

For the latest information on the drug profile of afatinib, please refer to the current Investigator's Brochure (IB) (U03-3218). All references in this protocol concerning afatinib refer to the free base compound afatinib which is used as the oral formulation.

Afatinib is moderately fast absorbed after oral administration. Maximum plasma concentrations of afatinib were achieved mainly at 2 to 5 hours after oral drug administration. Afatinib maximum plasma concentrations and area under the curve increased slightly over-proportional with increasing doses in the therapeutic range of 20-50 mg. Moderate to high inter- and intra-individual differences in plasma concentration were seen. Afatinib is highly distributed out of the blood and has a moderate to high clearance. The overall geometric mean terminal half-life at steady state was 37.2 hours in cancer patients. Steady state was reached no later than 8 days after the first administration. The major route of elimination of afatinib was via faeces. After food intake, a decreased systemic exposure was observed compared to administration under fasted conditions. Therefore, afatinib should be taken without food (i.e. food should not be consumed for at least 3 hours before and at least 1 hour after taking afatinib). The PK characteristics in Caucasian cancer patients were comparable to those observed in Japanese cancer patients.

Afatinib binds covalently to proteins to a variable extent and covalent protein adducts were the major circulating metabolites in the plasma. Afatinib did not show relevant inhibition or induction of cytochrome P450 isoenzymes, and it appears unlikely that drug-drug interactions based on this mechanism will occur.

Afatinib is a substrate of the P-gp transporter. Concomitant administration of the potent P-gp inhibitor ritonavir did not relevantly change the exposure to 40 mg afatinib when taken simultaneously with or 6 h after afatinib but increased the bioavailability of afatinib (single dose of 20 mg) by 48% and 39% for AUC_{0-∞} and C_{max} when given 1 h before afatinib, respectively. Pretreatment with the potent P-gp inducer rifampicin decreased the plasma exposure of 40 mg afatinib by 34 % afatinib (AUC_{0-∞}) and 22 % (C_{max}), respectively. Caution should be exercised when combining afatinib with potent P-gp modulators. In pre-clinical studies afatinib is not irritant to intact skin but an ocular irritant. Afatinib is mutagenic in a single bacteria strain, but did not show genotoxic potential in vivo when tested up to overt toxic/lethal doses. Studies on embryo-foetal development in rats and rabbits up to life-threatening doses have revealed no indication of teratogenicity.

Two phase I open label dose-escalation studies determined the MTD with continuous dosing of afatinib in patients with advanced solid tumours at 40 mg and 50 mg daily, respectively [10, 11]. Adverse events (AE) observed with afatinib are consistent with those reported for other EGFR and dual EGFR/HER2 inhibitors. The most frequent investigator defined drug-related AEs were associated with gastrointestinal disorders (including diarrhoea, and

stomatitis), skin and subcutaneous tissue disorders (rash, dry skin, pruritus, acneiform rash, acne), nail effects, epistaxis, fatigue and decreased appetite. Early and proactive management of diarrhoea, and skin rash together with treatment interruptions and dose reductions is recommended in line with recent guidelines in the management of common toxicities of EGFR and EGFR/HER2 TKIs and monoclonal antibodies [12-16].

4.5. Rationale for trial design

HER2 mutations are identified in about 2% of non-small-cell lung cancers (NSCLC) and appear to be critical for lung carcinogenesis. There are very few data available that describe the clinical course of *HER2* mutated NSCLC patients. Mazieres and colleagues recently retrospectively identified 65 NSCLC patients diagnosed with a *HER2* in-frame insertion in exon 20 [6]. The *HER2* mutation was almost an exclusive driver, except one single case with a concomitant *KRAS* mutation. The trial population presented with a median age of 60 years (range 31-86), a high proportion of women (45 vs. 20 men, 69%), and of never smokers (34, 52.3%). All tumours were adenocarcinomas and 50% were stage IV at diagnosis. For these latter cases, 22 anti-*HER2* treatments were administered after conventional chemotherapy in 16 patients. Subsequently, four progressive disease, seven disease stabilizations and eleven partial responses (overall response rate ORR 50%; disease control rate DCR 82%) were observed. Specifically, they observed a DCR of 93% for trastuzumab-based therapies (n = 15), 100 % DCR for afatinib (n = 3), but no response to other *HER2*-targeted drugs (n = 3). Progression free survival for patients with *HER2*-therapies was 5.1 months. Median survival was of 89.6 and 22.9 months for early stage and stage IV patients, respectively. This study, the largest to date dedicated to *HER2*-mutated NSCLC, reinforced the importance of screening for *HER2*-mutations in lung adenocarcinomas, and suggested the potential efficacy of *HER2*-targeted drugs in this population. Additionally, single case reports suggest that *HER2* mutations may be predictive for *HER2* targeting therapies in lung cancer [17-19]. Some ongoing clinical trials are enrolling patients with *HER2* mutated NSCLC, mixed together with *HER2* amplified or *EGFR* mutated NSCLC cases. Large biomarker screening programs such as the French National Program or the US Lung Cancer Mutation Consortium (LCMC) thus propose testing for *HER2* mutations.

4.6. Overall Risk/Benefit Assessment

Distinct subtypes of NSCLC are driven by a specific genetic alteration and are thus sensitive to inhibition of the corresponding activated oncogenic pathway. This new paradigm has substantially impacted lung cancer treatment: early treatment for advanced NSCLC consisted of chemotherapy tailored for patients according to the expected toxicity and more recently according to histologic subtype. Nowadays, NSCLC can be further subdivided into clinically relevant molecular subsets, according to their driving genetic alterations affecting tumour proliferation and survival.

HER2 mutations offer a new treatment strategy beyond the standard chemotherapy. Afatinib is a relatively well tolerated drug, for which we have rapidly learned to manage related toxicities. Biologically, its transversal inhibition of the ERB family receptor offers an

interesting blockade of interconnected cancer pathways and might prevent some early compensatory feedback or resistance mechanisms. Indeed, in the small series available to date, afatinib looks like being the most promising anti HER2 treatment. Based on available data, stabilization and response to afatinib is comparable or superior to classical second line chemotherapy (docetaxel), with a significantly better toxicity profile. This trial aims at confirming the role of afatinib in *HER2* mutated advanced NSCLC patients previously treated with platinum based chemotherapy.

Afatinib presents a manageable toxicity profile and potentially offers a significant activity in terms of disease control and long term outcome. Therefore this treatment option offers a good benefit to risk ratio in patients with *HER2*-mutated advanced NSCLC.

5. Objectives and endpoints

5.1. Primary objective

Evaluate the ability of afatinib to control disease in pretreated patients with advanced NSCLC harbouring *HER2* exon 20 mutations.

5.2. Secondary objectives

- 5.2.1. To evaluate secondary measures of clinical efficacy including progression free survival (PFS), objective response rate (ORR) and overall survival (OS).
- 5.2.2. To assess the safety and the tolerability of the treatment.

5.3. Primary endpoint

- 5.3.1. Disease control defined as complete or partial response, or disease stabilisation lasting at least 12 weeks (see section 14.1).

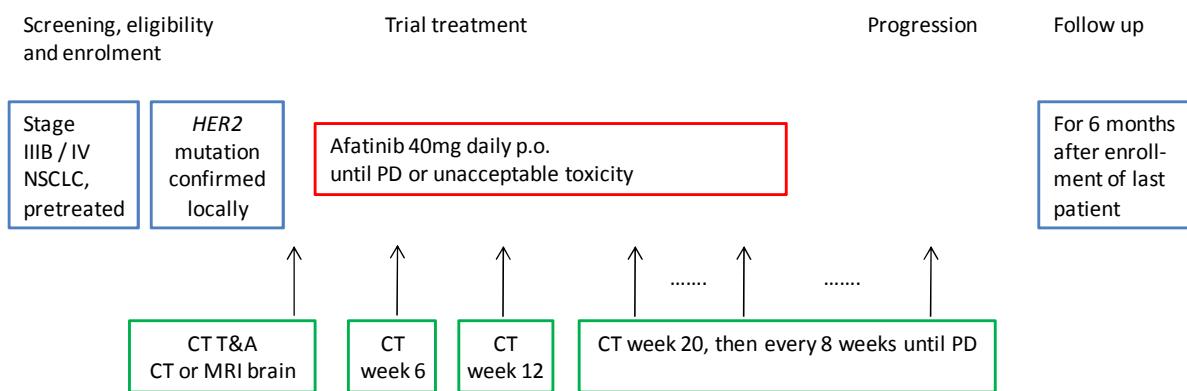
5.4. Secondary endpoints

- 5.4.1. Progression-free survival by RECIST 1.1
- 5.4.2. Objective response determined by RECIST 1.1
- 5.4.3. Overall survival
- 5.4.4. Adverse events graded according to CTCAE V4.0

For definitions, see section 14.

6. Trial design, duration and termination

This is a phase II, two-stage single-arm trial evaluating the efficacy of afatinib treatment in pretreated patients with advanced NSCLC harbouring *HER2* exon 20 mutations.



Participating sites will screen patients for *HER2* exon 20 mutations in their local laboratory. One FFPE tumor block must be sent to the central laboratory for later confirmation of the mutations.

Trial patients will receive afatinib 40 mg p.o./day until documented progression or unacceptable toxicity.

Patient accrual is expected to be completed within 24 months including a run-in-period of 6 months. Recruitment will not be stopped after enrolment of the first 9 patients into stage 1 of the 2-stage design. Follow-up will continue until 6 months from enrolment of the last patient. The final report will be prepared 40 months after the inclusion of the first patient. Trial duration is therefore expected to be 40 months.

Approximately six sites from five European countries will participate.

7. Patient selection

Written Informed Consent (IC) must be signed and dated by the patient and the investigator prior to any trial-related intervention or test for eligibility.

7.1. Inclusion criteria for enrolment

- 7.1.1. Histologically or cytologically confirmed non small cell lung cancer
- 7.1.2. Stage IIIB (non amenable to curative-intent multimodal treatment) or IV NSCLC, according to 7th TNM classification.
 - Contrast-enhanced CT of thorax and upper abdomen (incl. liver, kidney, adrenals);
 - brain MRI or CT

within 28 days before the date of enrolment.
- 7.1.3. Non-predominant squamous subtype (<50% squamous cells).
- 7.1.4. Previous treatment with a platinum based chemotherapy for advanced disease; or
Disease relapse or progression within <6 months after adjuvant platinum based chemotherapy, or (definitive) platinum-based chemo(radio)therapy for stage I-III NSCLC

7.1.5. Measurable or evaluable disease (according to RECIST 1.1 criteria). Not eligible: patients with only one measurable or evaluable tumour lesion which was resected or irradiated prior to enrolment.

7.1.6. Locally documented *HER2* mutation

7.1.7. Age \geq 18 years

7.1.8. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2 (see Table 1 below)

7.1.9. Life expectancy >3 months.

7.1.10. Adequate haematological function:

- WBC $\geq 2000/\mu\text{L}$
- haemoglobin $\geq 9\text{ g/dL}$
- neutrophils count $\geq 1.5 \times 10^9/\text{L}$
- platelet count $\geq 100 \times 10^9/\text{L}$

7.1.11. Adequate liver function:

- Total bilirubin $\leq 1.5 \times \text{ULN}$ (except subjects with Gilbert Syndrome, who can have total bilirubin $< 3.0\text{ mg/dL}$)
- ALT $< 2.5 \times \text{ULN}$
- AST $< 2.5 \times \text{ULN}$
- GGT $< 2.5 \times \text{ULN}$.

7.1.12. Adequate renal function: Calculated creatinine clearance $\geq 45\text{mL/min}$ (Cockcroft-Gault)

7.1.13. Patient capable of proper therapeutic compliance, and accessible for correct follow-up.

7.1.14. Women of childbearing potential (< 1 year without menstruation or < 2 years without menstruation following chemotherapy) must have a negative serum or urine pregnancy test within 7 days before beginning trial treatment.

7.1.15. Sexually active men and women of childbearing potential must use an effective contraceptive method (two barrier methods or a barrier method plus a hormonal method) during the trial treatment and for a period of at least 28 days following the last administration of trial drug.

7.1.16. Recovered from any previous therapy related toxicity to \leq Grade 1 at date of enrolment (except for recovery to \leq Grade 2 of alopecia, fatigue, creatinine increased, lack of appetite as well as stable sensory neuropathy)

- 7.1.17. Written Informed Consent (IC) for trial treatment must be signed and dated by the patient and the investigator prior to any trial-related intervention.
- 7.1.18. Tumour block available for central review of *HER2* mutation status.

Table 1. ECOG Performance Status

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

7.2. Exclusion criteria for enrolment

- 7.2.1. Patient with mixed small-cell and non-small-cell histologic features
- 7.2.2. Uncontrolled lepto-meningeal metastatic disease. Radiotherapy-treated or asymptomatic brain metastases are allowed (no systematic screening).
Patients with brain or subdural metastases are not eligible, unless they have completed local therapy and have discontinued the use of corticosteroids or have been on stable dose of corticosteroids for at least 4 weeks before starting trial treatment. Any symptoms attributed to brain metastases must be stable for at least 4 weeks before date of enrolment.
- 7.2.3. Previous treatment with *HER2* targeted antibody or tyrosine kinase inhibitor including afatinib.
- 7.2.4. Major surgery within 4 weeks before starting trial treatment or scheduled for surgery during the projected course of the trial.
- 7.2.5. Patient who has had in the past 3 years any previous or concomitant malignancy EXCEPT adequately treated basal or squamous cell carcinoma of the skin, *in situ* carcinoma of the cervix or bladder, *in situ* ductal carcinoma of the breast.
- 7.2.6. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of III or IV (see Table 2 below), unstable angina or poorly controlled arrhythmia as determined by the investigator. Myocardial infarction within 6 months prior to enrolment.

- 7.2.7. Patient with other serious diseases or clinical conditions, including but not limited to uncontrolled active infection and any other serious underlying medical processes that could affect the patient's capacity to participate in the trial.
- 7.2.8. Known HIV, active Hepatitis B or Hepatitis C infection (screening not required).
- 7.2.9. Known or suspected hypersensitivity to afatinib or any of its excipients.
- 7.2.10. Interstitial lung disease or pulmonary fibrosis.
- 7.2.11. Women who are pregnant or in the period of lactation.
- 7.2.12. Patients with any concurrent systemic anticancer therapy.
- 7.2.13. Any history or presence of poorly controlled gastrointestinal disorders that could affect the absorption of the trial drug (e.g. Crohn's disease, ulcerative colitis, chronic diarrhea, malabsorption).
- 7.2.14. Patient who received treatment with an investigational drug agent during the 3 weeks before enrolment in the trial.

Table 2. NYHA functional classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases

8. Patient screening and enrolment

This trial will use a web-based registration system. Each participating centre will access the system directly to enrol patients. Specific details for enrolment of patients are in the ***NICHE Procedures Manual*** which will be available on the ETOP website (www.etop-eu.org).

8.1. Screening

Note that written informed consent has to be obtained from the patient prior to any trial-specific intervention including any examination done specifically for screening purposes. The participating site should keep a screening log.

8.2. *HER2* mutation testing

The presence of *HER2* mutation needs to be confirmed according to the standard assay used in the local laboratory.

Appropriate molecular tests to detect clinically relevant *HER2* mutations should include direct sequencing of exon 20 of the *HER2* gene, validated PCR-based techniques, and clinically validated next generation sequencing methods, according to the standards of each laboratory. One block of FFPE material (or alternatively, 5-10 slides) from biopsy of primary tumor or metastatic lesion for each patient with *HER2* exon 20 mutation identified in the local laboratory will be subsequently sent for confirmation to the central laboratory at Medical University of Gdansk (Dr. Bartosz Wasag, Dept. of Biology and Genetics, Collegium Biomedicaum, Medical University of Gdansk, Poland), see ***NICHE procedures manual*** for details. This biological material will be stored at the central laboratory for potential targeted next generation sequencing that includes *HER2* and other lung cancer relevant driver mutations, such as EGFR, KRAS, ALK, ROS1, RET and BRAF. Clinical impact of other coexistent molecular alterations (if they are identified) would be analysed in exploratory analyses.

For the purpose of the patient enrolment into the trial, local testing is sufficient.

8.3. *Enrolment*

Verify eligibility, and then enrol the patient by entering the relevant information into the RDE facility ETOPdata according to the information in the ETOPdata User Manual. The date the Informed Consent was signed by the patient and the date signed by the investigator are both required to complete the eligibility checklist.

8.4. *Start of afatinib*

Afatinib treatment should start within 7 days after enrolment of the patient.

9. *Investigational product*

Afatinib is the Investigational Product (IP) used in this trial. Boehringer Ingelheim will provide the IP at no cost for the entire duration of this trial.

The ***Drug Supply Manual*** will describe detailed drug supply logistics as well as labelling, packaging, handling, drug accountability and destruction of unused drugs.

9.1. *Summary of the safety profile*

The types of adverse drug reactions (ADRs) were generally associated with the EGFR inhibitory mode of action of afatinib. The summary of all ADRs is shown in Table 3 below, with ADRs pooled from all NSCLC trials with daily afatinib doses of 40 mg (N=497) or 50 mg (N=1638) as monotherapy. The most frequent ADRs were diarrhoea and skin related adverse events as well as stomatitis and paronychia. Interstitial Lung Disease (ILD)-like adverse reactions were reported in 0.7% of afatinib treated patients. Overall, dose reduction led to a lower frequency of common adverse reactions.

In patients treated with once daily afatinib 40 mg, dose reductions due to ADRs occurred in 57% of the patients. Discontinuation due to ADRs diarrhoea and rash/acne was 1.3% and 0%, respectively.

Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome although in these cases there were potential alternative aetiologies.

Although rare, drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators and is considered an Adverse Event of Special Interest, see section 9.2.

Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to distinguish an effect of the underlying malignancy on liver function from other causes are important for patient safety.

Table 3. Summary of ADRs per frequency category

System organ class (CTCAE v.4)	Very common ($\geq 10\%$)	Common (1% to <10%)	Uncommon (0.1% to <1%)
Infections and infestations	Paronychia ¹	Cystitis	
Metabolism and nutrition disorders	Decreased appetite	Dehydration Hypokalaemia	
Nervous system disorders		Dysgeusia	
Eye disorders		Conjunctivitis Dry eye	Keratitis
Respiratory, thoracic and mediastinal disorders	Epistaxis	Rhinorrhoea	Interstitial lung disease
Gastrointestinal disorders	Diarrhea Stomatitis ²	Dyspepsia Cheilitis	
Hepatobiliary disorders		Alanine amino-transferase increased Aspartate amino-transferase incr.	
Skin and subcutaneous tissue disorders	Rash ³ Dermatitis acneiform ⁴ Pruritus ⁵ Dry skin ⁶	Palmar-plantar erythrodysesthesia syndrome	
Musculoskeletal and connective tissue disorders		Muscle spasms	
Renal and urinary disorders		Renal impairment / renal failure	
General disorders and administration site conditions		Pyrexia	
Investigations		Weight decreased	

1 – includes paronychia, nail infection, nail bed infection

2 – includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

3 – includes group of rash preferred terms

4 – includes acne, acne pustular, dermatitis acneiform

5 – includes pruritus, pruritus generalised

6 – includes dry skin, skin chapped

Very common ADRs in afatinib-treated patients occurring in at least 10% of patients in trial LUX-Lung 3 are summarised in Table 4:

Table 4. Very common ADRs in trial LUX-Lung 3

	Afatinib (40mg/day) N=229			Pemetrexed/Cisplatin N=111		
	Any grade	3	4	Any grade	3	4
NCI-CTC Grade						
MedDRA Preferred Term	%	%	%	%	%	%
<i>Infections and infestations</i>						
Paronychia ¹	57.6	11.4	0	0	0	0
<i>Metabolism and nutrition disorders</i>						
Decreased appetite	20.5	3.1	0	53.2	2.7	0
<i>Respiratory, thoracic and mediastinal disorders</i>						
Epistaxis	13.1	0	0	0.9	0.9	0
<i>Gastrointestinal disorders</i>						
Diarrhoea	95.2	14.4	0	15.3	0	0
Stomatitis ²	69.9	8.3	0.4	13.5	0.9	0
Cheilitis	12.2	0	0	0.9	0	0
<i>Skin and subcutaneous tissue disorders</i>						
Rash ³	70.3	14.0	0	6.3	0	0
Dermatitis acneiform ⁴	34.9	2.6	0	0	0	0
Dry skin ⁵	29.7	0.4	0	1.8	0	0
Pruritus ⁶	19.2	0.4	0	0.9	0	0
<i>Investigations</i>						
Weight decreased	10.5	0	0	9.0	0	0

1 – Includes Paronychia, Nail infection, Nail bed infection

2 – Includes Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Oral mucosa erosion, Mucosal erosion, Mucosal ulceration

3 – Includes group of rash preferred terms

4 – Includes Acne, Acne pustular, Dermatitis acneiform

5 – Includes Dry skin, Skin chapped

6 – Includes Pruritus, Pruritus generalised

9.2. Adverse Events of Special Interest

Drug-induced liver injury (DILI):

- For patients with normal liver function at baseline:
Hepatic injury defined by an elevation of AST and/or ALT >3 × ULN combined with an elevation of bilirubin $>2 \times \text{ULN}$ measured in the same blood draw sample.
- For patients with impaired function tests at baseline:
Hepatic injury defined by an elevation of AST and/or ALT >5 × ULN combined with an elevation of bilirubin $>2 \times \text{ULN}$ measured in the same blood draw sample.

Adverse Events of Special Interest are to be reported in an expedited manner like Serious Adverse Events, even if they do not meet any of the seriousness criteria. Please submit the completed SAE Initial Report Tab in the RDE system within 24 hours after awareness of the event, and choose “yes” in the “description” section if this is a “non-serious adverse event of special interest”. Please submit the SAE Follow-up Report within 14 days after the Initial Report.

10. Trial treatment

10.1. Administration

Treatment with afatinib 40 mg p.o./day should start within 7 days after enrolment of the patient.

Afatinib should be taken without food, approximately at the same time of the day. Food should not be consumed for at least 3 hours before and at least 1 hour after taking this medicinal product.

The tablets should be swallowed whole with water. If swallowing of whole tablets is not possible, these can be dispersed in approximately 100 ml of noncarbonated drinking water. No other liquids should be used. The tablet should be dropped into the water without crushing it, and stirred occasionally for up to 15 min until it is broken up into very small particles. The dispersion should be consumed immediately. The glass should be rinsed with approximately 100 ml of water which should also be consumed. The dispersion can also be administered through a gastric tube.

Missed dose:

If a dose is missed, it should be taken within the same day as soon as the patient remembers. However, if the next scheduled dose is due within 8 hours then the missed dose must be skipped.

Patient diary:

The patient should document each self-administration of afatinib on the patient diary.

10.2. Delay and dose modification for toxicity

Treatment related toxicities will be managed by treatment interruptions and subsequent dose reductions of afatinib according to the schedule described in Table 5. Dose reductions will apply to individual patients only. Once the dose has been reduced, it cannot be increased later.

To prevent the development of more severe adverse events, treatment related diarrhoea, nausea and vomiting or rash should be managed early and proactively as described in Section 11.3.

Table 5. Dose reduction scheme for afatinib

AE type and CTCAE Grade	Action	Dose reduction scheme
<u>Events related to trial drug:</u> <ul style="list-style-type: none"> • Diarrhoea Grade 2 persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/ hydration • Reduced renal function to \geq Grade 2 as measured by serum creatinine, proteinuria or decrease in glomerular filtration rate of more than 50% from baseline • Any drug related AE Grade ≥ 3 	Pause treatment until patient has recovered to Grade ≤ 1 or baseline ¹ . Resume treatment at reduced dose according to dose reduction scheme (next column). If patient has not recovered to Grade ≤ 1 or baseline ¹ within 14 days, trial treatment must be permanently discontinued ² .	If patient was receiving 40 mg, resume treatment at a dose of 30 mg. If patient was receiving 30 mg, resume treatment at a dose of 20 mg. If patient was receiving 20 mg, discontinue afatinib.
Acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever)	Pause afatinib while clinical assessment to exclude ILD is completed.	If ILD is ruled out as a cause of symptoms, grade symptoms and relatedness and report as AEs. If AEs are not related, resume afatinib at current dose. If AEs are drug related, follow instructions in row above. If ILD is confirmed, discontinue afatinib

1 – Baseline is defined as the CTCAE Grade at the start of treatment

2 – In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib will be decided in agreement between ETOP and the investigator.

Adverse reactions of grade 1 should not lead to interruption or dose reduction.

Similarly, adverse reactions of grade 2 but not prolonged (i.e. <48h of diarrhea and <7 days of rash) should not lead to interruption or dose reduction. See section 11.3 for management of diarrhea and section 11.4 for management of dermatological adverse reactions.

In case of any unrelated adverse events, the investigator may choose to interrupt the medication for up to 14 days, but no dose reduction should occur. If the medication is interrupted for more than 14 days, the decision to continue with afatinib will be made by ETOP in agreement with the investigator; please contact NICHE@etop-eu.org.

If the medication is interrupted for more than a cumulative interval of 3 weeks, the decision to continue with afatinib will be made by ETOP in agreement with the investigator; please contact NICHE@etop-eu.org.

11. Management of adverse events, concomitant therapy, restrictions and rescue treatment

11.1. Rescue medication, emergency procedures, and additional treatment(s)

11.1.1. Rescue medication

Rescue medications to reverse the actions of afatinib are not available. There is no specific antidote for overdosage with afatinib. Potential adverse events should be treated symptomatically. Common adverse events of treatment with afatinib with specified management recommendations and/or requirements include diarrhoea, and rash/acne. To improve tolerability and the probability of clinical benefit, patients should receive prompt and appropriate supportive care at the first signs of symptoms. Suggested treatments for AEs are described below.

11.1.2. Concomitant treatment(s)

Concomitant medications or therapy to provide adequate supportive care may be given as clinically necessary.

After trial enrollment, palliative radiotherapy may be given for bone pain or for other reasons (e.g. bronchial obstruction, skin lesions), provided that the total dose delivered is in a palliative range according to institutional standards. The irradiated area can not be used for tumour response assessment. During palliative radiotherapy, trial treatment should be delayed and may be resumed once the patient has recovered from any radiation associated toxicity. If medication is interrupted for more than 14 days, the decision to continue will be made by ETOP in agreement with the investigator; please contact NICHE@etop-eu.org. Continuous interruption of >28 days due to palliative radiotherapy will not be allowed.

All concomitant therapy, including anaesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, must be recorded in the eCRF during the screening and treatment period, starting from the date of signature of informed consent, and ending at the

EOT visit. After the EOT visit, only concomitant therapy indicated for treatment of an AE has to be reported.

In case of major elective surgery (as judged by the investigator), it is recommended to stop treatment with afatinib one week prior to the surgery, and to restart treatment after complete wound healing. If afatinib is interrupted for more than 14 days, the decision to continue will be made by ETOP in agreement with the investigator.

11.1.3. Emergency procedures

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude interstitial lung disease (ILD). Trial drug should be interrupted pending investigation of these symptoms. If interstitial lung disease is diagnosed, trial drug must be permanently discontinued and appropriate treatment instituted as necessary.

Patients who present with symptoms of keratitis, such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmic specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with afatinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment with afatinib should be carefully considered. Afatinib should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is a risk factor for keratitis and ulceration.

11.2. Management of expected adverse events

Dermatologic adverse events and diarrhoea are the most common side-effects associated with treatment with afatinib. Treatment of these side-effects should be proactive and should be started as early as possible after onset of symptoms.

11.3. Management of diarrhoea and dehydration

Diarrhoea occurs at a high frequency and generally begins within 2 weeks of exposure to afatinib. Although usually mild to moderate, diarrhoea may lead to dehydration and compel treatment modification or discontinuation, so early management is essential (Table 6). At the time of initiation of treatment with afatinib patients should be given a supply of loperamide to keep with them at all times or access to loperamide should be confirmed; and patients should be counselled on the appropriate use of loperamide.

Patients must be advised to drink an adequate amount of fluids to make up for the fluid lost through diarrhoea.

Table 6. Grade specific treatment recommendations for afatinib related diarrhoea

Severity (CTCAE Grading)	Description	Intervention concerning afatinib treatment	Specific intervention
Mild (Grade 1)	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue same dose	Stop laxatives and advise patient to drink at least 8-10 glasses of water or clear fluids per day; 4 mg (2 tablets) of loperamide to be taken immediately, followed by 2 mg (1 tablet) after each loose stool until bowel movements cease for 12 hours
Moderate (Grade 2)	Increase of 4-6 stools per day over baseline; i.v. fluids indicated < 24 hours; moderate increase in ostomy output compared with baseline; not interfering with ADL	Continue same dose unless Grade 2 diarrhoea continues for \geq 2 days (48 hours) in which case treatment must be interrupted until recovered to \leq Grade 1 followed by dose reduction*	Continue loperamide; assess for dehydration and electrolyte imbalance; consider IV fluids and electrolyte replacement
Severe (Grade 3)	Increase of \geq 7 stools per day over baseline; incontinence; IV fluids > 24 hours; hospitalisation; severe increase in ostomy output compared with baseline; interfering with ADL	Dose interruption until recovered to \leq Grade 1 followed by dose reduction*	See Grade 2; plus: an infectious process should be ruled out with stool cultures; aggressive iv fluid replacement \geq 24 hours; hospitalisation to monitor progress; consider prophylactic antibiotics if patient is also neutropenic;
Life threatening (Grade 4)	Life-threatening consequences (e.g. haemodynamic collapse)	Dose interruption until recovered to \leq Grade 1 followed by dose reduction*	See Grade 3

* If despite optimal supportive care and a treatment interruption, diarrhoea does not resolve to CTC AE Grade \leq 1 within 14 days, treatment with afatinib must be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib will be decided in agreement between ETOP and the investigator.

11.4. Management recommendations for dermatological AEs

Dermatologic AEs of afatinib include rash, acne, dermatitis acneiform, and dry skin. General recommendations for prophylaxis are summarized in Table 7 and grade-specific treatment recommendations are summarized in Table 8. For dose adjustment of afatinib refer to Table 5 section 10.2.

Specific interventions should be reassessed at least after 2 weeks or at any worsening of symptoms, in which case the specific intervention should be adjusted and, depending on own clinical experience, early involvement of a dermatologist should be considered.

Table 7. General recommendations for prophylaxis while receiving afatinib

Personal hygiene	<p>Use of gentle soaps and shampoos for the body, e.g. pH5 neutral bath and shower formulations and tepid water.</p> <p>Use of very mild shampoos for hair wash.</p> <p>Only clean and smooth towels are recommended because of potential risk of infection. The skin should be patted dry after a shower, whereas rubbing the skin dry should be avoided.</p> <p>Fine cotton clothes should be worn instead of synthetic material.</p> <p>Shaving has to be done very carefully.</p> <p>Manicure, i.e. cutting of nails, should be done straight across until the nails no longer extend over the fingers or toes. Cuticles are not allowed to be trimmed because this procedure increases the risk of nail bed infections</p>
Sun protection	<p>Sunscreen should be applied daily to exposed skin areas regardless of season. Hypoallergenic sunscreen with a high SPF (at least SPF30, PABA free, UVA/UVB protection), preferably broad spectrum containing zinc oxide or titanium dioxide are recommended</p> <p>Patients should be encouraged to consequently stay out of the sun.</p> <p>Protective clothing for sun protection and wearing a hat should be recommended.</p>
Moisturizer treatment	<p>It is important to moisturize the skin as soon as anti-EGFR therapy is started. Hypoallergenic moisturizing creams, ointments and emollients should be used once daily to smooth the skin and to prevent and alleviate skin dryness.</p> <p>Note: avoid greasy creams (e.g. petrolatum, soft paraffin, mineral oil based) and topical acne medications</p>
Prevention of paronychia	<p>Patients should keep their hands dry and out of water if ever possible.</p> <p>They should avoid friction and pressure on the nail fold as well as picking or manipulating the nail.</p> <p>Topical application of petrolatum is recommended around the nails due to its lubricant and smoothing effect on the skin.</p>

Table 8. Grade specific treatment recommendations of skin reactions to afatinib

Severity (CTCAE Grading)	Description	Specific intervention
ACNEIFORM RASH		
Mild (Grade 1)	Macular or papular eruptions or erythema without associated symptoms	<p>Consider topical antibiotics, e.g. clindamycin 2% or topical erythromycin 1% cream or metronidazole 0.75% or topical nadifloxacin 1%;</p> <p>Isolated scattered lesion: cream preferred</p> <p>Multiple scattered areas: lotion preferred</p>

Severity (CTCAE Grading)	Description	Specific intervention
Moderate (Grade 2)	Macular or papular eruptions with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of BSA	Topical treatment as for Grade 1 ¹ plus short term topical steroids, e.g. prednicarbate cream 0.02% plus an oral antibiotic (for at least 2 weeks) e.g. Doxycycline 100mg b.i.d. or Minocycline hydrochloride 100mg b.i.d
Severe (Grade 3)	Severe, generalized erythroderma or macular, popular or vesicular eruption; desquamation covering ≥ 50% of BSA; associated with pain, disfigurement, ulceration or desquamation	Topical and systemic treatment as for Grade 2. ¹ Consider referral to dermatologist Consider systemic steroids
Life threatening (Grade 4)	Generalized exfoliative, ulcerative, or bullous dermatitis	See Grade 3 Systemic steroids are recommended
EARLY AND LATE XEROTIC SKIN REACTIONS – PRURITUS		
Mild (Grade 1)	Mild or localized	Topical polidocanol cream. Consider oral antihistamines, e.g. diphenhydramine, dimethindene, cetirizine, levocetirizine, desloratadine, fexofenadine or clemastine)
Moderate (Grade 2)	Intense or widespread	See Grade 1 plus oral antihistamines; Consider topical steroids, e.g. topical hydrocortisone
Severe (Grade 3)	Intense or widespread and interfering with activities of daily living (ADL)	See Grade 2.
XEROSIS (DRY SKIN)		
Mild (Grade 1)	Asymptomatic	Soap-free shower gel and/or bath oil. Avoid alcoholic solutions and soaps. Urea- or glycerin-based moisturizer. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Severe (Grade 3)	Symptomatic, interfering with ADL	See Grade 2. Topical steroids of higher potency (e.g. prednicarbate, mometasone furoate) Consider oral antibiotics
FISSURES		

Severity (CTCAE Grading)	Description	Specific intervention
Mild (Grade 1)	Asymptomatic	<p>Petroleum jelly, Vaseline® or Aquaphor for 30 minutes under plastic occlusion every night, followed by application of hydrocolloid dressing; antiseptic baths (e.g. potassium permanganate therapeutic baths, final concentration of 1:10,000, or povidone-iodine baths)</p> <p>Topical application of aqueous silver nitrate solutions to fissures</p>
Moderate (Grade 2)	Symptomatic, not interfering with ADL	<p>See Grade 1.</p> <p>Consider oral antibiotics.</p>
Severe (Grade 3)	Symptomatic, Interfering with ADL	See Grade 2.
1 If Grade 2 rash persists for ≥ 7 days despite treatment and is poorly tolerated by the patient, the investigator may choose to pause treatment up to 14 days followed by a reduction in the dose of afatinib according to the dose reduction scheme in Table 5		

11.5. Management of mucositis/stomatitis

General and grade specific recommendations are described in Table 9. For dose adjustment refer to Table 5 and for restrictions on concomitant therapies refer to Sections 11.6.

Treatment is supportive and aimed at symptom control. These may include atraumatic cleansing and rinsing with non-alcoholic solutions such as normal saline, diluted salt and baking soda solution (e.g. one-half teaspoonful of salt and one teaspoon of baking soda in one quart of water every four hours); avoidance of agents containing iodine, thyme derivatives and prolonged use of hydrogen peroxide; dietary manoeuvres such as promotion of soft, non irritating foods like ice-creams, mashed/cooked vegetables, potatoes and avoidance of spicy, acidic or irritating foods such as peppers, curries, chillies, nuts and alcohol. If the patient is unable to swallow foods or liquids, parenteral fluid and/or nutritional support may be needed. Examples of some of the agents suggested in Table 9 include: topical analgesics – viscous lidocaine 2%; mucosal coating agents – topical kaolin/pectin; oral antacids, maltodextrin, sucralfate; topical antifungals – nystatin suspension (adapted from [20]).

Table 9. Grade specific treatment recommendations of trial-drug related mucositis/stomatitis

Severity (CTCAE grading)	Description	Treatment recommendations	Intervention concerning afatinib treatment / dose modification
Mild (Grade 1)	Minimal symptoms; normal diet	Oral rinses with agents such as non-alcoholic mouth wash, normal saline, diluted salt and baking soda solution .	No change .
Moderate (Grade 2)	Symptomatic, but can eat and swallow modified diet	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis.	Maintain dose if tolerable; Hold dose if intolerable until recovery to grade ≤ 1 , then restart at the same dose.
Severe (Grade 3)	Symptomatic and unable to adequately aliment or hydrate orally	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated .	Hold dose until recovery to grade ≤ 1 or baseline, then restart at the reduced dose according to Table 5.
Life threatening (Grade 4)	Symptoms associated with life-threatening consequences	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated	Hold dose until recovery to grade ≤ 1 or baseline, then restart at the reduced dose according to Table 5

11.6. Restrictions

11.6.1. Restrictions regarding concomitant treatment

Additional experimental anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment (with the exception of megestrol acetate and use of anti-androgens and/or gonadorelin analogues for treatment of prostate cancer), or radiotherapy (other than palliative radiotherapy for symptom control) is not allowed concomitantly with the administration of trial treatment.

Afatinib is a substrate of the P-gp (permeability glycoprotein) transporter. Caution should be exercised when combining afatinib with P-gp modulators.

Table 10. List of potent inhibitors and inducers of P-glycoprotein (MDR1)

Inhibitors	Inducers
Amiodarone	Carbamazepine
Azithromycin	Phenytoin
Captopril	Rifampicin
Carvedilol	St John's Wort
Clarithromycin	Phenobarbital Salt
Conivaptan	Tipranavir
Cyclosporine	Ritonavir
Diltiazem	
Dronedarone	
Erythromycin	
Felodipine	
Itraconazole	
Ketoconazole	
Lopinavir	
Nelfinavir	
Ritonavir	
Quinidine	
Ranolazine	
Saquinavir	
Tacrolimus	
Ticagrelor	
Verapamil	

The information on potent inhibitors and inducers of P-glycoprotein may evolve. It is important for the investigator to record the administration of such modulators on the concomitant medications form.

11.6.2. Restrictions on diet and life style

Patients should be advised to avoid any foods known to aggravate diarrhoea.

To prevent skin related adverse events it is recommended to avoid intense irradiation with UV light and harsh detergents, see also Section 11.4.

11.7. Women of Child-Bearing Potential and Pregnancy Prevention

Female patients who are not of childbearing potential due to being postmenopausal (1 year without menstruations without an alternative medical cause or at least 2 years without menstruation following chemotherapy) or surgically sterilised (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception to be eligible for the trial.

All other patients are considered to be of childbearing potential and must use adequate contraception throughout the trial (from screening until end of trial participation or at least 28 days after last dose of trial medication, whichever is later).

Acceptable methods of contraception include surgical sterilisation and double barrier method, and must be in accordance with local regulations where applicable. Double barrier method of contraception is defined as two barrier methods used simultaneously each time

the patient has intercourse. Accepted barrier methods include diaphragm, female condom, cervical cap, male condom and intrauterine device (IUD) (the diaphragm and cervical cap must be used in conjunction with spermicidal jelly/cream). Those using hormonal contraceptives, or with partners using hormonal contraceptives, must also be using an additional approved method of contraception (as described above). Partner vasectomy, natural "rhythm" and spermicidal jelly/cream are not acceptable methods of contraception.

Similarly, male patients must use acceptable methods of contraception mentioned above.

Women who become pregnant while participating in the trial must discontinue trial medication immediately. The pregnancy must be reported following procedures detailed in section 12.2.1

11.8. Treatment compliance

The trial medication will be given in accordance with the protocol and the instructions of a site investigator.

The appropriate number of afatinib tablets for treatment cycles (3 weeks for the first four cycles, then 4 weeks) will be provided to patients to be self-administered at home. Patients should be instructed to use the Patient Diary to record every self-administration as well as any symptoms and to bring the Patient Diary to every visit at the clinic.

Patients will be asked to bring the remaining trial medication at the end of each cycle to the investigator site for a compliance check. The remaining film-coated tablets will be counted by the investigator/site staff and recorded at the investigator site. Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken as well as the information recorded in the patient diary must be documented and explained. At the end of each cycle, any remaining medication will be collected. If the patient is eligible for further treatment, a new bottle of trial medication must be dispensed.

The investigator and/or ETOP can withdraw a patient from the trial in the event of serious and persistent non-compliance which jeopardizes the patient's safety or render trial results for this patient unacceptable. Patients who do not attend a minimum of 75% of scheduled trial visits, unless due to exceptional circumstances, should be discussed with ETOP and be evaluated for compliance.

11.9. Treatment duration

Patients remain on treatment until one of the following events, whichever occurs first:

- Documented progression according to RECIST v1.1
- Secondary malignancy resulting in need of systemic treatment
- Unacceptable toxicity
- Medical condition that prevents further treatment
- Patient withdraws consent
- Patient becomes pregnant
- Trial treatment interrupted for too long

- Patient is not compliant with protocol

If the IP has been stopped for any reason, the patient enters the follow-up phase of the trial. Patients who discontinue trial treatment should be assessed by the investigator who must document the case on the appropriate CRF.

12. Adverse events and reporting

12.1. Adverse event reporting

The main criterion for tolerability is the occurrence of toxicities and adverse events. The severity and causality will be classified according to the NCI CTCAE Version 4. The CTCAE is available for downloading on the internet (<http://evs.nci.nih.gov/ftp1/CTCAE/About.html>).

An adverse event is defined as any untoward medical occurrence that occurs from the date of informed consent until 90 days after the final dose of afatinib, regardless of whether it is considered related to the trial treatment. The relationship of the adverse event with the administered trial treatment has to be indicated (unrelated – unlikely – possible – probable – definite).

In addition, any known untoward event that occurs subsequent to the adverse event reporting period that the investigator assesses as possibly related to the protocol treatment should be considered an adverse event.

Symptoms of the targeted cancer (if applicable) and hospitalisations for the management of the underlying disease should not be reported as adverse events.

The adverse event severity grade provides a qualitative assessment of the extent or intensity of an adverse event, as determined by the investigator or as reported by the subject. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure), and does not reflect the relationship to trial drug.

Severity grade for other adverse events not covered in the toxicity grading scale:

1 = Grade 1	Mild
2 = Grade 2	Moderate
3 = Grade 3	Severe
4 = Grade 4	Life-threatening
5 = Grade 5	Fatal

Note:

- Report the highest grade observed within one period.
- Baseline symptoms will be recorded on the CRF and changes in grade as well as resolution of an AE during treatment have to be reported.
- Laboratory abnormalities for non-safety parameters will be documented on the AE CRF from grade ≥ 3 only

- AEs should not be reported in a narrative description.

12.2. Definition of Serious Adverse Event (SAE)

12.2.1. SAEs during trial treatment

An SAE is defined in general as any undesirable medical occurrence/adverse drug experience that occurs during or within 90 days after stopping trial treatment that results in any of the following:

- is fatal (any cause except progression of disease)
- life-threatening,
- requires or prolongs inpatient hospitalisation,
- results in persistent or significant disability/incapacity
- is a congenital anomaly or birth defect
- is a secondary malignancy
- is a medically important event
- Overdose, only if associated with a symptom or AE

Second (non-NSCLC) malignancies are always considered SAEs, no matter when they are diagnosed. These events should be reported on the Serious Adverse Event Forms.

Other significant/important medical events which may jeopardise the patient are also considered serious adverse events.

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Serious also includes any other event that the investigator or the ETOP Safety Office judges to be serious or which is defined as serious by the regulatory agency in the country in which the event occurred.

An unexpected adverse event is one that is not listed as a known toxicity of the investigational drug in the summary of product characteristics.

A related adverse event is one for which the investigator assesses that there is a reasonable possibility that the event is related to the investigational drug. All adverse events judged as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.

Events not considered to be serious adverse events are hospitalisations occurring under the following circumstances:

- elective surgery;
- occur on an outpatient basis and do not result in admission (hospitalisation < 24 h);
- are part of the normal treatment or monitoring of the studied treatment;
- progression of disease (by convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs,

even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting).

12.2.2. SAEs after end of trial treatment

For 90 days after stop of afatinib, the following events have to be reported as SAE:

- fatal, life-threatening and other medically significant events possibly, probably or definitely related to late effects of trial treatment
- disabling events
- second primary cancer
- congenital anomaly

In the case of pregnancy occurring during trial treatment or within 1 year after treatment discontinuation, the investigator shall immediately notify this by completing the pregnancy reporting form. The investigator shall ensure that the case is followed up to the end of the pregnancy and supply a final report on the outcome.

12.3. Definition of Serious Adverse Reaction (SAR)

SARs are all SAEs considered to be related (possibly, probably, definitely) to the trial treatment.

12.4. Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious adverse reaction that is assessed as unexpected on the basis of the applicable Swiss product information, the European summary of product characteristics, and the Investigators' Brochure.

12.5. Reporting SAEs and Adverse Events of Special Interest

Drug-induced liver injuries as defined in section 9.2 are considered to be Adverse Events of Special Interest (AESIs) and are to be reported on the SAE form, within 24 hours of awareness.

Following the subject's written consent to participate in the trial, all SAEs, whether related or not related to trial drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 90 days of discontinuation of dosing.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods that is suspected to be related to trial drug or protocol-specified procedure.

Any SAE or AESI must be reported by submitting the completed SAE Initial Report Tab in the RDE system within 24 hours of awareness.

Submission is done via the remote data entry system, or in case of unavailability, by sending the SAE form by fax to the ETOP Safety Office:

+41 31 389 92 29

Once the remote data entry system is available again, the SAE Tab has to be completed by the site.

The SAE/AESI outcome must be reported within 14 days after onset by online submitting the SAE/AESI Follow-up Report Tab. In case the SAE is reported as ongoing after 14 days, the follow-up report has to be submitted again with the final outcome.

The ETOP Safety Office will forward each SAE to the trial chairs and notify principal investigators of any SAR meeting the criteria for expedited reporting (SUSAR) within the timelines specified in GCP.

The local Ethics Committee must be informed by the principal investigator about SAEs according to local regulations.

The ETOP Safety Office will inform Boehringer Ingelheim Regional Drug Safety and other appropriate persons about all SAEs and AESIs at least possibly related to trial medication (per either investigator or ETOP Safety Office review) within 24 hours of receipt.

The ETOP Safety Office will record the SAE and prepare an annual safety report (DSUR, Development Safety Update Report). Listings of SAEs will be prepared as required.

12.6. Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a patient is pregnant or may have been pregnant at the time of investigational product exposure, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must inform ETOP within 24h of awareness by completing and submitting the Pregnancy Form in ETOPdata.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Form.

In case the pregnancy is associated with a serious adverse event (fetal death, congenital anomaly, abortion, complication requiring hospitalisation), this has to be reported on the SAE form within 24h.

Any pregnancy that occurs in a female partner of a male trial participant should be reported to ETOP. Information on this pregnancy will be collected on the Pregnancy Form.

13. Response evaluation

13.1. RECIST 1.1 criteria

The patient's response to protocol treatment will be assessed by RECIST 1.1 criteria (see appendix 2).

13.2. Determination of time point response

Table 11. Determination of time point response

Target lesions	Non-target lesions	New lesions	Resulting Overall response
CR	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE unless the sum of diameters of <i>evaluated</i> lesions indicates PD ¹⁾
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

- 1) From ref. 1 in Appendix 2, p.234: 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 50mm 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.

13.3. Determination of best overall response

Best overall response is defined as best response across all time points. Confirmation of partial or complete response by an additional scan is not requested in this trial. Response at week 6 assessment will be confirmed by the week 12 assessment; response at week 12 assessment will be confirmed by the week 20 assessment.

14. Endpoints definition

14.1. Disease control

This is the primary endpoint. It is defined as complete or partial response, or disease stabilisation lasting at least 12 weeks.

14.2. Progression-free survival

This is defined as the time from the date of enrolment until documented progression or death, if progression is not documented. Censoring will occur at the last tumour assessment only if patient is lost to follow-up.

14.3. Objective response

Objective response is defined as best overall response (CR or PR) across all assessment time-points during the period from enrolment to termination of trial treatment. Objective response to afatinib treatment will be determined using RECIST 1.1 criteria (see section 13).

14.4. Overall survival

Defined as time from the date of enrolment until death from any cause. Censoring will occur at the last follow-up date.

14.5. Toxicity

Adverse events classified according to NCI CTCAE version 4.

15. Trial procedures

This section gives an overview of procedures, clinical and laboratory evaluations and follow-up investigations.

15.1. Baseline evaluations (within 28 days prior to enrolment)

The following examinations should be done within a maximum of 28 days before enrolment. If examinations were done prior to 28 days before enrolment, they have to be repeated.

- 15.1.1. Obtain written informed consent prior to any trial-specific evaluations or interventions
- 15.1.2. Local *HER2* mutation testing (test may have been done prior to 28 days)
- 15.1.3. Medical history including symptoms, smoking history, medications, comorbidities and allergies
- 15.1.4. Physical examination according to local standards, including blood pressure [mmHg], ECOG performance status, body weight [kg]
- 15.1.5. Haematology: WBC, haemoglobin, platelets, neutrophils. Needs to be repeated

prior to first dose of afatinib if done more than 7 days prior to first dose.

- 15.1.6. Chemistry: sodium (Na), potassium (K), calcium, albumin, magnesium. Needs to be repeated prior to first dose of afatinib if done more than 7 days prior to first dose.
- 15.1.7. Renal function: serum creatinine and creatinine clearance calculated according to Cockcroft-Gault
- 15.1.8. Hepatic function: ALT, AST, bilirubin, GGT
- 15.1.9. Electrocardiogram
- 15.1.10. Pregnancy test for women of childbearing potential within 7 days before trial treatment start
- 15.1.11. CT thorax and upper abdomen. PET-CT thorax and upper abdomen can be used instead of CT scan if contrast-enhanced
- 15.1.12. Brain MRI or CT
- 15.1.13. Ascertain availability of FFPE tumour material for later central review of *HER2* mutation

15.2. At trial treatment start visit

Week 0 is the week of trial treatment start. The following evaluations should be done at the week 0 visit:

- 15.2.1. If not done within 7 days prior to first dose, repeat haematology and chemistry *before* first dose: WBC, haemoglobin, platelets, neutrophils; sodium, potassium, calcium, albumin, magnesium (to be reported on baseline form)
- 15.2.2. Record current symptoms, and all adverse events which have occurred after signing informed consent, on adverse event CRF
- 15.2.3. Record all concomitant medication from date of signed informed consent.

15.3. During first 3 weeks of afatinib treatment

- 15.3.1. Regular contact with patient to monitor adverse events, especially diarrhoea (phone contact allowed) according to treatment tolerability and investigator's decision.

15.4. Every visit during afatinib treatment

Visits will take place at 3, 6, 9 and 12 weeks after first dose, then every 4 weeks until stop of treatment.

- 15.4.1. Physical examination according to local standards, including blood pressure, performance status, and body weight
- 15.4.2. Check patient diary and count remaining tablets

- 15.4.3. Recording of symptoms / adverse events
- 15.4.4. Haematology: WBC, haemoglobin, platelets, neutrophils
- 15.4.5. If clinically indicated according to local standards: Chemistry; sodium (Na), potassium (K), calcium, albumin, magnesium
- 15.4.6. Serum creatinine and creatinine clearance calculated according to Cockcroft-Gault
- 15.4.7. Hepatic function: ALT, AST, bilirubin, GGT
- 15.4.8. Record all concomitant medication
- 15.4.9. Give to the patient the afatinib tablets for the next treatment cycle (3 or 4 weeks)

15.5. Imaging

The following imaging will be done on weeks 6 and 12 from day of first dose of trial treatment, and then every 8 weeks (weeks 20, 28, 36 etc) until progression:

- 15.5.1. CT thorax and upper abdomen

15.6. End of treatment visit

At the end of all trial treatment and **irrespective of the reason for stopping treatment**, an end of treatment visit at the centre is to be scheduled within 30 days following the last dose of trial treatment or within 30 days after planned treatment start if treatment never started. This visit has to be done for all patients, including those who did not start afatinib treatment. The following procedures should be performed:

- 15.6.1. Physical examination according to local standards, performance status, and body weight
- 15.6.2. Recording of symptoms / adverse events
- 15.6.3. Haematology: WBC, haemoglobin, platelets, neutrophils
- 15.6.4. Chemistry: sodium (Na), potassium (K), calcium, albumin, magnesium
- 15.6.5. Serum creatinine and creatinine clearance calculated according to Cockcroft-Gault
- 15.6.6. Hepatic function: ALT, AST, bilirubin, GGT
- 15.6.7. Pregnancy test for women of childbearing potential
- 15.6.8. CT thorax and upper abdomen, if not done within the last 6 weeks
- 15.6.9. Record all concomitant medication

15.7. Follow up after treatment stop, before progression

Follow up visits after trial treatment stop but before progression will take place every 8 weeks until progression; and should be scheduled at the same time as the CT scans

- 15.7.1. Report any pregnancy occurring within 6 months after treatment stop
- 15.7.2. Report any adverse event occurring within 90 days after treatment stop
- 15.7.3. Report any concomitant medication within 90 days after treatment stop

15.8. Follow up after progression

Follow up visits after progression will take place every 3 months until death or until 6 months from enrolment of the last patient, whatever occurs first.

- 15.8.1. Record survival status
- 15.8.2. Report any pregnancy occurring within 6 months after treatment stop
- 15.8.3. Report any adverse event occurring within 90 days after treatment stop
- 15.8.4. Report any concomitant medication within 90 days after treatment stop

16. Case report forms and documentation

16.1. Case report forms schedule

CRFs will only be available on-line at the Remote Data Entry (RDE) facility ETOPdata. No paper forms will be used, with the exception of paper SAE initial and follow-up forms in case of system unavailability.

Table 12. Case report forms

Tab in ETOPdata	To be completed
Eligibility for Enrolment	Within 28 days of start of baseline assessments
Baseline	Until 7 days after start of afatinib
Concomitant Medication	Continuously from signed informed consent to 90 days after end of trial treatment Within 7 days after each afatinib visit.
Trial Treatment Start Visit	Within 7 days after trial treatment start visit.
Afatinib Treatments	Within 7 days of the end of each cycle
Tumour Assessment	Baseline: Within 7 days after start of afatinib; Within 14 days after every imaging (weeks 6, 12 after start of afatinib treatment, and then every 8 weeks until progression)

Tab in ETOPdata	To be completed
Adverse Events	<p>Continously from signed informed consent to 90 days after end of afatinib treatment:</p> <p>Within 7 days after <i>enrolment</i> (to record symptoms present at enrolment);</p> <p>Within 7 days after each afatinib treatment visit;</p> <p>End of treatment: Within 14 days after end-of-treatment visit if patient has been treated with afatinib.</p> <p>In follow-up for 90 days after treatment stop</p>
Pregnancy	<p>Within 24h of first documentation of pregnancy;</p> <p>Within 14 days of end of pregnancy.</p>
Serious Adverse Event Initial Report	<p>Within 24h of awareness of SAE or AESI;</p> <p>Can be submitted via ETOPdata or via fax to ETOP Safety Office in case of unavailability of ETOPdata.</p>
Serious Adverse Event Follow-up Report	<p>Within 14 days of completion of initial report.</p> <p>If event was not resolved after 14 days, submit an additional report again within 7 days of resolution/final outcome of event.</p>
End of Treatment	<p>Within 14 days after end of treatment visit (which is to take place within 30 days after end of treatment)</p>
Follow-up	<p>To be completed within 14 days after each follow-up visit and at death.</p>

Consult the ***CRF completion guideline*** for detailed instructions on how to complete, save and submit the electronic CRFs.

17. Statistical considerations

17.1. Primary objective

To evaluate the ability of afatinib to control disease in pretreated patients with advanced NSCLC harbouring *HER2* exon 20 mutations. Disease control is defined as complete or partial response, or disease stabilisation lasting at least 12 weeks.

17.2. Sample size determination

For sample size determination, a Simon's two stage phase II design [21] is adopted. A Disease Control Rate (DCR) of 50% is considered as unacceptable, targeting a DCR of 75%. Hence the null hypothesis under consideration is that the $DCR \leq 50\%$ versus the alternative that $DCR \geq 75\%$. For a one-sided type I error of 10% and power of 80%, a total of

22 patients need to enter the trial, with 9 patients in the first stage. If in the first stage, 6 out of the 9 patients achieve Disease Control, then the trial will proceed to the second stage and recruit an additional 13 patients for a total of 22 patients. If at the end of trial, at least 14 patients achieve Disease Control, then this finding will indicate that it would be reasonable to proceed to a Phase III trial.

17.3. Evaluation of primary and secondary objectives

The total trial duration will be approximately 40 months including a 6 months start-up period, 24 months accrual, 6 months follow-up after inclusion of the last patient, and 4 months for preparation of the final trial report.

The final evaluation of the trial will be performed approximately 40 months after the inclusion of the first patient.

The binomial exact one-sample test will be used for evaluation of the primary endpoint (DCR) at both the interim and final analysis (if trial continues to completion) [22-25]. The conclusion will be based on examining whether or not the observed number of patients who have achieved complete response, partial response and stable disease crosses the corresponding O'Brien-Fleming boundary. Results will be presented in terms of rates together with the corresponding exact binomial 90% confidence intervals.

The secondary endpoints of Progression free survival (PFS) and overall survival (OS) will be estimated by the Kaplan Meier method. Clinical efficacy will also be described by objective response rate (ORR).

Safety and tolerability of the afatinib treatment will be presented by tabulation of the CTCAE V4 grade. The safety cohort will encompass all patients who have received at least one dose of trial treatment.

Statistical analysis of both the primary and secondary endpoints will be described in detail in the Statistical Analysis Plan (SAP) document

17.4. Early stopping rules

An early look will take place at the end of the first stage, when 9 patients are evaluable for the primary endpoint. This report will be submitted to the Independent Data Monitoring Committee (IDMC), see section 20.3. If less than 6 patients achieve Disease Control, then the results will be reported immediately and the Steering Committee will decide whether the patients still on treatment should stop it. Otherwise the trial will continue as planned until the final evaluation. The recruitment into the trial will continue during the preparation of the analysis of the first stage.

18. Criteria for termination of the trial

18.1. General criteria for termination of the trial

The trial may be discontinued early in parts or completely if the information on the product leads to doubt as to the benefit/risk ratio, by decision of ETOP or Trial Steering Committee, or at the suggestion of the IDMC based on the interim safety evaluations.

The trial can be terminated at any time if the authorization and approval to conduct the trial is withdrawn by Ethics Committee or regulatory authority decision, insufficient accrual, emerging new data impacting the scientific value of the trial or ethical grounds.

18.2. Discontinuation of protocol treatment for individual patients

Protocol treatment should be stopped in the following situations:

- Disease progression.
- Occurrence of unacceptable toxicities. Stopping protocol treatment is determined by medical judgment of the treating physician.
- Inter-current severe illnesses which would in the judgment of the investigator affect assessments of the clinical status to a significant degree and require discontinuation of protocol therapy. Note: Diagnosis of another neoplastic disease (second malignant tumour) does not mandate a stop of trial therapy; patients may continue to receive protocol treatment after appearance of a second primary tumour, stopping protocol treatment is determined by the medical judgment of the treating physician.
- Request by the patient. Patients have the right to refuse further trial treatment at any time during the trial. Such patients will remain in the trial and will be transferred to the follow-up phase.
- If a patient refuses to have the treatments or follow-up examinations and tests needed to determine whether the treatment is safe and effective.

The decision for discontinuation of protocol treatment of individual patients is taken by the treating physician based on his medical evaluation and taking into account the patient's individual situation.

18.3. Withdrawal of consent

Patients have the right to withdraw consent for further trial participation at any time without having to specify the reason. The data recorded up to the timepoint of withdrawal will continue to be evaluated in the trial. The investigator should ask the patient for consent to continue to collect information on her/his disease and survival status.

It should be documented in both the medical records and in the eCRF, according to the instructions in the ***CRF completion guidelines***, if the patient accepts to be contacted for survival status despite withdrawing the trial consent. For the patient's safety, an end of treatment visit should be performed and documented in the eCRF.

19. Ethics aspects, regulatory approval, and Patient Informed Consent

The Investigator will ensure that this trial is conducted in full conformance with the principles of the “Declaration of Helsinki” or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in “Guideline for Good Clinical Practice” ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC).

19.1. Ethical Review Board/Ethics Committee

All protocols and the patient informed consent forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The ERB/IRB decision must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent.

The ERB/IRB written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent. Documentation of Ethics Committee approval must be sent to the ETOP Coordinating Office prior to enrolment of the first patient.

Any modifications made to the protocol must be submitted to the appropriate ERB/IRB for information or approval in accordance with local procedures and regulatory requirements and to Health Authorities if required.

Once approved or acknowledged by the appropriate ERB/IRB and by the Health Authorities (if required), the investigator shall implement the protocol modifications. Protocol modifications for urgent safety matters may be directly implemented following the instructions of ETOP.

19.2. Regulatory approval procedures

If applicable, in addition to the approval of the Ethics Committee according to national legislation, the protocol, other protocol related documents including patient information and informed consent and other documents as required locally must be submitted to and be approved by the health authority. Documentation of health authority approval must be sent to the ETOP Coordinating Office prior to Participating Centre activation.

19.3. Informed consent

Informed consent for each patient will be obtained prior to initiating any trial procedures in accordance with the “Patient Information and Informed Consent” (See Appendix I). One signed and dated copy of the informed consent must be given to each patient and the original copy must be retained in the investigator's trial records. The informed consent form must be available to monitors and in the case of data audits. Verification of signed informed consent and the date signed are required for inclusion to this trial.

The "Declaration of Helsinki" recommends that consent be obtained from each potential patient in biomedical research trials after the aims, methods, anticipated benefits, and potential hazards of the trial, and discomfort it may entail, are explained to the individual by the physician. The potential patient should also be informed of her/his right to not participate or to withdraw from the trial at any time. The process of obtaining the informed consent must be documented in the patient record.

If the patient is in a dependent relationship to the physician or gives consent under duress, the informed consent should be obtained by an independent physician. By signing this protocol, the investigator agrees to conduct the trial in accordance with Good Clinical Practice and the "Declaration of Helsinki."

ETOP recognises that each institution has its own local, national, and international guidelines to follow with regard to informed consent. Therefore, we provide a template information sheet and informed consent form (Appendix I), which can be edited to incorporate information specific to your institution. The template Patient Information Sheet and Informed Consent has been written according to ICH guidelines which state the Informed Consent should adhere to GCP and to the ethical principles that have origin in the "Declaration of Helsinki". The final version needs to receive the Institutional Review Board/ Local Ethics Committee approval in advance of its use. Centres need to send their locally modified PIS/IC to ETOP for review and approval before submitting to their Ethics Committee.

20. Governance and administrative issues

20.1. Final report

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

20.2. Steering Committee

A Steering Committee will be constituted for this trial. The Steering Committee is responsible for maintaining the scientific integrity of the trial, for example, by recommending changes to the protocol in light of emerging clinical or scientific data from other trials. Membership will include the trial chair and co-chair, trial coordinators, trial statisticians, ETOP officials, representatives from some participating institutions and groups, and a representative from Boehringer Ingelheim.

20.3. Independent Data Monitoring Committee

The trial will be presented for review to the ETOP IDMC at each of their semi-annual meetings. Accrual and safety will be monitored. The Stage 1 Report will be reviewed by the IDMC which will make a recommendation to continue or stop the trial based on the results.

20.4. Publication

The results of the trial will be published according to the ETOP publication policy.

20.5. Clinical trial insurance

ETOP will contract the appropriate liability insurance for this trial. Patients who suffer injuries due to the trial should report them immediately to their physician. The local group/institution should report all alleged claims immediately to the ETOP Coordinating Office.

20.6. Quality Assurance

ETOP conducts trials according to the ICH Good Clinical Practice (GCP) guidelines. The Trial Data Manager reviews each CRF as it is received. In addition, the ETOP Medical Reviewer reviews each case at specific timepoints. ETOP conducts periodic audit visits to ensure proper trial conduct, verify compliance with GCP, and perform source data verification.

The Investigator should ensure that source documents are made available to appropriately qualified personnel from ETOP or its designees, or to Ethics Committee and health authority inspectors after appropriate notification.

At regular intervals during the clinical trial, the centre will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review trial progress, investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, dispensing IP, compliance with protocol, drug accountability, concomitant therapy use, and quality of data.

20.7. Protocol adherence

Investigators ascertain that they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact ETOP or personnel monitoring the trial to request approval of a protocol deviation, as no deviations are permitted. The investigator should document and explain any deviations from the approved protocol. The investigator should promptly report any deviations to ETOP and to the EC concerned in accordance with the applicable EC policies and procedures. If the investigator feels a protocol deviation would improve the conduct of the trial this must be considered a protocol amendment, and unless such an amendment is developed and activated by ETOP and approved by the IRB/IEC/REB it cannot be implemented. All protocol deviations will be recorded.

20.8. Data protection

The samples and data collected will be coded to protect patient confidentiality. Each patient will have a unique identifier assigned by the RDE facility ETOPdata. Sites are responsible to keep a patient log locally in order to be able to link the unique identifier to the record of the patient.

Biological material will be assigned the same unique identifier. No identifiable / personal data will be stored in the trial database or the tissue repositories in the central lab.

Biological material will be transferred outside the treating institution for central review. Results of the assays will be coded only by the patient identifier.

Regulatory authorities and pertinent Ethics Committees (IRB/ERB) may have access to patient data on-site. ETOP audit or monitoring personnel will also have access to such data on-site.

20.9. Record Retention

The centre must retain all essential documents according to ICH GCP. This includes copies of the patient trial records, which are considered as source data, patient informed consent statement, laboratory printouts, drug inventory and destruction logs, and all other information collected during the trial. These documents are to be stored until at least 15 years after the termination of the trial. ETOP guarantees access and availability of the data entered into ETOPdata for at least 15 years after the termination of the trial.

Longer retention may be required for participating centres according to national regulations.

In the event that the Principal Investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer has to be given to ETOP and the local Ethics Committee at least one month in advance.

21. References

1. Jemal, A., et al., *Global cancer statistics*. CA Cancer J Clin, 2011. **61**(2): p. 69-90.
2. National, C.I.B., *SEER Cancer Statistics Review, 1975-2006*. Available at http://seer.cancer.gov/csr/1975_2006, 2009.
3. Schiller, J.H., et al., *Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer*. N Engl J Med, 2002. **346**(2): p. 92-8.
4. Spector, N.L. and K.L. Blackwell, *Understanding the mechanisms behind trastuzumab therapy for human epidermal growth factor receptor 2-positive breast cancer*. J Clin Oncol, 2009. **27**(34): p. 5838-47.
5. Perera, S.A., et al., *HER2YVMA drives rapid development of adenosquamous lung tumors in mice that are sensitive to BIBW2992 and rapamycin combination therapy*. Proc Natl Acad Sci U S A, 2009. **106**(2): p. 474-9.
6. Mazieres, J., et al., *Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives*. J Clin Oncol, 2013. **31**(16): p. 1997-2003.
7. Arteaga, C.L., et al., *Treatment of HER2-positive breast cancer: current status and future perspectives*. Nat Rev Clin Oncol, 2012. **9**(1): p. 16-32.
8. Gatzemeier, U., et al., *Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer*. Ann Oncol, 2004. **15**(1): p. 19-27.
9. Arcila, M.E., et al., *Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas*. Clin Cancer Res, 2012. **18**(18): p. 4910-8.
10. Ould-Kaci, M., *Investigator's brochure. Afatinib (BIBW 2992). Version 14, 1200.P1 - 1200.P10*., 2013.
11. Temple, G., S. Bell, and P. Stopfer, *A Phase I open-label dose escalation study of continuous once-daily oral treatment with BIBW 2992 in patients with advanced solid tumours. Trial 1200.3*. . 2010.
12. Lynch, T.J., Jr., et al., *Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management*. Oncologist, 2007. **12**(5): p. 610-21.
13. Lacouture, M.E., et al., *Dermatologic adverse events associated with afatinib: an oral ErbB family blocker*. Expert Rev Anticancer Ther, 2013. **13**(6): p. 721-8.
14. Yang, J.C., et al., *Diarrhea associated with afatinib: an oral ErbB family blocker*. Expert Rev Anticancer Ther, 2013. **13**(6): p. 729-36.
15. Moy, B. and P. Goss, *Lapatinib-associated toxicity and practical management recommendations*. Oncologist 1007. **12**(7): p. 756-765.
16. Giaccone, G., B. Melosky, and M. Reck, *Epidermal growth factor receptor inhibitor (EGFR)-associated rash: a suggested novel management paradigm. A consensus position from the EGFR dermatologic toxicity forum*., in *ECCO2007*: Barcelona.
17. Cappuzzo, F., L. Bemis, and M. Varella-Garcia, *HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer*. N Engl J Med, 2006. **354**(24): p. 2619-21.
18. De Greve, J., et al., *Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu*. Lung Cancer, 2012. **76**(1): p. 123-7.
19. Tomizawa, K., et al., *Prognostic and predictive implications of HER2/ERBB2/neu gene mutations in lung cancers*. Lung Cancer, 2011. **74**(1): p. 139-44.
20. Porta, C., et al., *Management of adverse events associated with use of everolimus in patients with advanced renal cell carcinoma* . Eur J Cancer, 2011. **47**: p. 1287-1298.

21. Simon, R., *Optimal two-stage designs for phase II clinical trials*. Control Clin Trials, 1989. **10**(1): p. 1-10.
22. Corporation, C.S., *EaSt: a software package for the design and interim monitoring of group sequential clinical trials*. , 2011, Cytel Software Corporation, Cambridge, MA.
23. Fleming, T.R., *ONE-SAMPLE MULTIPLE TESTING PROCEDURE FOR PHASE-II CLINICAL-TRIALS*. Biometrics, 1982. **38**(1): p. 143-151.
24. Jennison, C. and B.W. Turnbull, *Group sequential designs with applications to clinical trials*. 2000: Chapman & Hall/CRC, Boca Raton.
25. Schultz, J.R., et al., *Multiple-stage procedures for drug screening*. Biometrics, 1973. **29**(2): p. 293-300.