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BELIEF

ETOP 2-11

An open-label phase II trial of erlotinib and bevacizumab in patients with advanced non-small cell lung cancer and activating EGFR mutations

Bevacizumab and ErLotinib In EGFR mut+ NSCLC

A clinical trial of ETOP

Coordinated by Grupo Español de Cancer de Pulmón GECP (Spanish Lung Cancer Group)

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Version 2.0

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In collaboration with Hoffmann-La Roche

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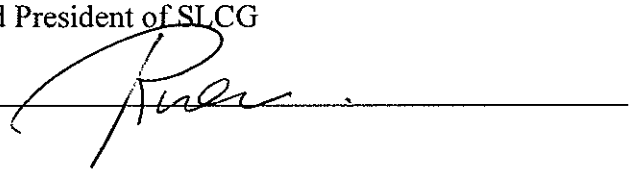

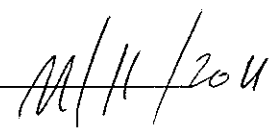

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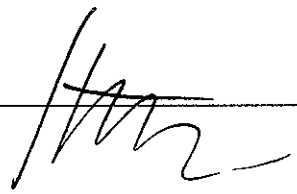

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Date

Protocol Signature Page Amendment 1

ETOP 2-11 BELIEF

Approved by:

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25/Nov 2013

Date

Rolf Stahel
Trial Co-Chair and Chairman of ETOP

25.11.13

Date

Principal Investigator Protocol Signature Page

BELIEF

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. 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

Principal Investigator Protocol Signature Page for Amendment 1

ETOP 2-11 BELIEF

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

A phase II trial of erlotinib and bevacizumab in patients with advanced non-small cell lung cancer and activating EGFR mutations

Rationale: Advanced non-small-cell lung cancer (NSCLC) patients harbouring epidermal growth factor receptor (EGFR) mutations (del19 or L858R) show an impressive progression-free survival between 9 and 14 months when treated with erlotinib. However, the presence of EGFR mutations can only imperfectly predict outcome. We hypothesize that progression-free survival could be influenced both by the pretreatment EGFR T790M mutation and by components of DNA repair pathways.

We propose a model of treatment whereby patients with EGFR mutations (single or with T790M) can attain a benefit with longer overall PFS when treated with erlotinib plus bevacizumab. When the patients are grouped by BRCA1 mRNA levels and T790M the hypothesis is that the combination of erlotinib plus bevacizumab can improve the PFS in all subgroups.

Objectives:

1. To determine long-term outcome of patients with advanced non-squamous NSCLC harbouring EGFR mutations with or without T790M mutation at diagnosis and treated with the combination of erlotinib and bevacizumab. Primary endpoint: progression-free survival
2. To evaluate the efficacy and tolerability of the combination
3. To evaluate the correlation of BRCA1 mRNA and AEG-1 mRNA expression and T790M with progression-free survival
4. To monitor EGFR mutations (including T790M) in serum and plasma longitudinally
5. To evaluate molecular biomarkers related to EGFR TKI and bevacizumab

Design: This is a multinational, multi-center phase II trial of erlotinib plus bevacizumab in patients with advanced non-squamous NSCLC harbouring EGFR mutations confirmed by central re-assessment. Patients will be stratified into two subgroups, with and without EGFR T790M mutation. The stratification will be done after the inclusion of patients.

Sample size: 102 patients

Most important eligibility criteria:

1. non-squamous cell, non-small-cell lung cancer
2. metastatic disease or locally advanced and not amenable for radical surgery or radiotherapy
3. centrally confirmed EFGR mutation (exon del19 or L858R)
4. Measurable or evaluable disease (according to RECIST 1.1 criteria)
5. Age ≥ 18 years
6. Adequate haematological, renal and hepatic function

Trial treatment: Bevacizumab: 15 mg/kg i.v. on day 1 of each 3-week cycle

Erlotinib: 150 mg p.o., daily

Cycles of 3 weeks until progression

Statistical considerations:

The trial consists of two phase II substudies run in parallel, and requires 102 patients, with 35 patients with EGFR T790M mutation enrolled in substudy 1, and 67 patients without EGFR T790M mutation enrolled in substudy 2. The first substudy follows Simon's two-stage design and a decision can be reached at the first stage, while the second substudy follows Fleming's single stage design. Patients not EGFR mutated at central review will stop treatment. These patients will be excluded from final efficacy analysis, and will be documented as ineligible. Ineligible patients will be replaced to reach the total sample size, per study design. Patients who have been recruited into the trial but are not evaluable for efficacy will be replaced (up to 10% of total sample size).

Duration: The total duration of the trial will be approximately 48 months, with an accrual period of 12 months including run-in period of 3 months, accrual and total follow-up of 36 months. The clinical database and the central tissue bank will be kept for an unlimited time.

The trial will end with the preparation of the final report, scheduled for month 54 after the inclusion of the first patient. Trial subjects will receive trial medication up to 18 months after the inclusion of the last patient. All patients who are still benefiting from their treatment at that time have to be switched to commercial drug which will be reimbursed by Roche.

Translational research:

Formalin-fixed, paraffin-embedded tissue will be collected from all enrolled patients. EGFR mutation status will be centrally determined or confirmed. T790M will be analyzed as soon as the complete patient sample has been enrolled into the trial. BRCA1 mRNA expression and AEG-1 will be evaluated where enough tissue is available.

Serum and plasma samples will be collected at baseline, after 6 weeks (time of first tumor evaluation), and at the time of progression. They will be used to search for molecular alterations corresponding to the tumor tissue. Samples will be stored locally at -80ºC and shipped in batches to the central laboratory.

2. Flow charts

2.1. Graphical trial design

2.2. Trial schedule

	Screening [1]	≤ 28 days prior enrolment	At enrolment	Cycle 1	Cycles 2, 4, ... (even cycles)	Cycles 3, 5, ... (odd cycles)	At progression	End of treatment visit [4]	Follow-up[6]
Days			0	1	22,64,...	43,85,...			
Weeks			0	1	4,10,...	7,13,...			
Written informed consent [2]	X								
Medical history	X								
Tumour material [1]	X								
Blood sample [4]			X			X [4]	X		
Physical exam, PS, blood pressure, weight		X		X	X	X		X	X
Baseline symptoms		X							
Haematology		X		X	X	X		X	
Renal function: serum creatinine, urine dipstick		X		X	X	X		X	
Hepatic function: ALT, AST, AP, Bilirubin		X		X	X	X		X	
Coagulation: INR		X							
Pregnancy test if applicable		X							
Tumour assessment [3]		X				X	X	X [5]	X
Adverse events				X	X	X		X	
Bevacizumab				X	X	X			
Erlotinib (daily)				X	X	X			
Second-line therapy									X

1 – screening must be done within 28 days before treatment start; tumour material from biopsy and/or original surgery

2 – before any trial-specific intervention

3 – CT of thorax and abdomen prior to start of cycles 3, 5, 7, 10, 13, 16, 20, 24, 28; in case of treatment discontinuation without progression weeks 6, 12, 18, 27, 36, 45, 57, 69, 81 and every 12 weeks until progression. CT scan of brain is not mandatory and only recommended in case of clinically suspected brain metastasis.

4 – Serum and plasma samples for translational research should be taken at baseline, after 6 weeks (time of first tumor evaluation), and at the time of progression.

5 – For patients who discontinued study treatment due to toxicity rather than progressive disease, restaging (CT scan chest and abdomen, brain scan if applicable) should be repeated if not already performed within 30 days prior to the last dose of study treatment

6- Patients who discontinue treatment before progression should be assessed at the same timepoints as patients still on treatment, weeks 6, 12, 18, 27, 36, 45, 57, 69, 81; and then every 12 weeks until progression (see section 16.7). Patients with progression should be assessed every 12 weeks (see section 16.10).

3. List of abbreviations

AEG-1	astrocyte elevated gene 1
ALT	Alanine transaminase
AP	Alkaline phosphatase
AST	Aspartate transaminase
BRCA1	breast cancer 1, early-onset
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EGFR	epidermal growth factor receptor
FFPE	formalin fixed, paraffin embedded
INR	International Normalized Ratio
LLN	lower limit of normal lab value
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
RDE	remote data entry
RECIST	Response Evaluation Criteria In Solid Tumours
ULN	upper limit of normal lab value
VEGF	vascular endothelial growth factor

4. Background and Rationale

4.1. EGFR mutations in lung cancer

Lung cancer is the leading cause of death from cancer in Europe (1). The most common type of lung cancer is adenocarcinoma, followed by squamous cell carcinoma, large cell carcinoma and small cell carcinoma. More than two thirds of patients with lung cancer are diagnosed with advanced, inoperable disease. Until recently, the mainstay of treatment for these patients was platinum-based chemotherapy, regardless of tumor histology (2).

Activating mutations in exon 19 and 21 of the epidermal growth factor receptor gene (EGFR) confer hypersensitivity to the tyrosine kinase inhibitors erlotinib and gefitinib in patients with advanced NSCLC (3, 4, 5). The Spanish Lung Cancer Group (SLCG) previously evaluated the feasibility of large-scale screening for EGFR mutations in patients with NSCLC, and analyzed the association between the mutations and the outcome of erlotinib treatment (6). From April 2005 through November 2008, lung cancers from 2105 patients in 129 institutions in Spain were screened for EGFR mutations. The analysis was performed in a central laboratory. Patients with tumors carrying EGFR mutations were eligible for erlotinib treatment. EGFR mutations were found in 350 of 2105 patients (16.6%). Mutations were more frequent in women (69.7%), in patients who had never smoked (66.6%), and in those with adenocarcinomas (80.9%) ($P<0.001$ for all comparisons). The mutations were deletions in exon 19 (62.2%) and L858R (37.8%). Median progression-free survival and overall survival for 217 patients who received erlotinib were 14 months and 27 months, respectively. This study demonstrated that large-scale screening of patients with lung cancer for EGFR mutations is feasible and can have a role in decisions about treatment.

The SLCG conducted the prospective randomized phase III trial EURTAC comparing erlotinib with platinum-based chemotherapy in chemonaive patients with advanced NSCLC harboring EGFR mutations. From February 2007 to January 2011, 1227 patients were screened for EGFR mutations, and 174 patients were randomly assigned to receive erlotinib or platinum-based chemotherapy. The primary endpoint was progression-free survival (PFS). Secondary endpoints included response, overall survival and toxicity profiles. Preliminary results of the interim analysis were presented at ASCO 2011 (7). One hundred and fifty-three patients (76 chemotherapy, 77 erlotinib) were evaluable for the interim analysis. Patient characteristics in the chemotherapy arm were: 16 males; median age, 64; never smokers, 56; PS 0, 26; PS 1, 41; adenocarcinoma, 67. Patient characteristics in the erlotinib arm were: 25 males; median age, 65; never smokers, 54; PS 0, 23; PS 1, 44; adenocarcinoma, 73. Response rate was 10.5% to chemotherapy versus 54.5% to erlotinib ($P<0.0001$). PFS in the chemotherapy arm was 5.2 months (95%CI, 4.4-5.8 months) compared to 9.4 months (95%CI, 7.9-12.3 months) in the erlotinib arm (HR, 0.42; $P<0.0001$). Median survival was 18.8 months in the chemotherapy arm and 22.9 months in the erlotinib arm (HR, 0.80; $P=0.42$).

In the pan-Asian phase III trial IPASS, gefitinib was superior to carboplatin-paclitaxel as an initial treatment for pulmonary adenocarcinoma among nonsmokers or former light smokers in East Asia. The presence in the tumor of a mutation of the EGFR gene was a strong predictor of a better outcome with gefitinib (8). The North-East Japan, West Japan and first-SIGNAL trials confirmed the superiority of gefitinib over chemotherapy for progression free survival in Asian patients with activating EGFR mutations (9). The phase III trial OPTIMAL in China compared erlotinib versus chemotherapy with carboplatin and

gemcitabine in 83 patients with a confirmed EGFR exon 19 deletion or exon 21 L858R mutation (10). Median progression-free survival was significantly longer in erlotinib-treated patients than in those on chemotherapy (13.1 [95% CI 10.58-16.53] versus 4.6 [4.21-5.42] months; hazard ratio 0.16, 95% CI 0.10-0.26; p<0.0001). Chemotherapy was associated with more grade 3 or 4 toxic effects than was erlotinib (including neutropenia and thrombocytopenia), while the most common grade 3 or 4 toxic effects with erlotinib were increased alanine aminotransferase concentrations and skin rash. Chemotherapy was also associated with increased treatment-related serious adverse events.

Based on the results of EURTAC and the Asian trials, frontline therapy with an EGFR inhibitor has become a new standard-of-care for patients with advanced NSCLC and activating EGFR mutations (11).

4.2. Mechanisms of tumor resistance to erlotinib: T790M and DNA-repair

In contrast to activating EGFR mutations, the T790M mutation in EGFR exon 20 is associated with resistance to EGFR inhibitors (12). The role of other resistance factors including diverse and complex molecular signal pathways (MET, Src, AKT and others) is less well understood and we focused our previous research on DNA-repair pathways. We hypothesized that progression-free survival could be influenced both by the pretreatment EGFR T790M mutation and by the expression of BRCA1. BRCA1 (breast cancer 1, early onset) repairs DNA double-strand breaks by homologous recombination (13). Experimental evidence suggested that BRCA1 overexpression enhances sensitivity to docetaxel and resistance to cisplatin. (14). We assessed the T790M mutation in pretreatment diagnostic specimens from 129 erlotinib-treated advanced NSCLC patients with EGFR mutations (15). The expression of eight genes and two proteins involved in DNA repair and four receptor tyrosine kinases was also examined. The EGFR T790M mutation was observed in 45 of 129 patients (35%). Progression-free survival was 12 months in patients with and 18 months in patients without the T790M mutation (P=0.05). Progression-free survival was 27 months in patients with low BRCA1 mRNA levels, 18 months in those with intermediate levels, and 10 months in those with high levels (P=0.02). In the multivariate analysis, the presence of the T790M mutation (hazard ratio [HR], 4.35; P=0.001), intermediate BRCA1 levels (HR, 8.19; P<0.0001), and high BRCA1 levels (HR, 8.46; P<0.0001) emerged as markers of shorter progression-free survival. Low BRCA1 levels neutralized the negative effect of the pretreatment EGFR T790M mutation and were associated with longer progression-free survival to erlotinib.

To prospectively examine the effect of EGFR mutations and BRCA1 mRNA levels in patients with advanced NSCLC, we conducted a prospective non-randomized phase II clinical trial, testing the hypothesis that customized therapy would confer improved outcome over non-customized therapy (16). We treated 123 metastatic NSCLC patients using a customized approach. RNA and DNA were isolated from microdissected specimens from paraffin-embedded tumor tissue. Patients with EGFR mutations received erlotinib, and those without EGFR mutations received chemotherapy with or without cisplatin based on their BRCA1 mRNA levels: low, cisplatin plus gemcitabine; intermediate, cisplatin plus docetaxel; high, docetaxel alone. Median survival exceeded 28 months for 12 patients with EGFR mutations, and was 11 months for 38 patients with low BRCA1, 9 months for 40 patients with intermediate BRCA1, and 11 months for 33 patients with high BRCA1. Two-year survival was 73.3%, 41.2%, 15.6% and 0%, respectively. In an exploratory analysis, we also examined the effect of RAP80 and Abraxas, which form a complex and are required for the DNA damage reponse (17). Median survival was influenced by RAP80 expression in the three BRCA1 groups. For example, for patients with both low BRCA1 and low RAP80,

median survival exceeded 26 months. RAP80 was a significant factor for survival in patients treated according to BRCA1 levels (hazard ratio, 1.3 [95% CI, 1-1.7]; P = 0.05).

AEG-1 (astrocyte elevated gene 1) is a multifunctional oncogene that plays a role in several carcinogenic processes. Through PI3K/Akt, AEG-1 activates IKK, leading to phosphorylation and destabilization of the NF-kB inhibitor NFKBIA, which is a gatekeeper for EGFR signaling (18, 19). We analyzed BRCA1/AEG-1 in 55 erlotinib-treated EGFR mutated NSCLC patients (20). Tumor mRNA expression levels of BRCA1 and AEG-1 were assessed by quantitative PCR in 77 erlotinib-treated patients with EGFR mutations. Expression levels were dichotomized at the median. PFS was longer in patients with low AEG-1 expression (27 vs 12 months; P=0.003). Median survival (MS) was not reached for patients with low AEG-1 levels and was 24 m for patients with high levels (P=0.08). Based on these results, we generated an AEG-1/BRCA1 risk model: patients with high levels of both genes were considered high-risk, patients with low levels of both genes were low-risk, and patients with high levels of one and low levels of the other gene were intermediate-risk. PFS was not reached in the low-risk group, while it was 18 months for the intermediate-risk group and 8 months for the high-risk group (P=0.00006) (hazard rate HR for high- vs low-risk groups, 6.6; 95%CI, 2-4-18; P<0.00001). Median survival was not reached in the low-risk group, while it was 31 months for the intermediate-risk group and 18 months for the high-risk group (P=0.05). In the multivariate analysis for PFS, the only independent prognostic variables were bone metastases (HR, 2.7; 95%CI, 1.1-6.5; P=0.03) and the AEG-1/BRCA1 risk groups (HR for high-risk group, 7.7 (95%CI, 2.8-21.3; P<0.00001).

BARD1 (BRCA1 associated RING domain protein 1) couples with BRCA1 and, together with the E3 ubiquitin ligases RNF8, RNF168 and RAP80, is essential for DNA repair (20). We examined BARD1 expression in 55 EGFR-mutant NSCLC patients treated with erlotinib (22). CodeSets (Reporter and Capture probe sets) for 48 genes were custom-designed by NanoString Technologies. BARD1 levels were significantly associated with PFS: low, 23 months; high, 6 months (P=0.03). We generated an AEG-1/BARD1 risk model: patients with high levels of both genes were considered high-risk, patients with low levels of both genes were low-risk, and patients with high levels of one and low levels of the other gene were intermediate-risk. PFS was not reached in the low-risk group, while it was 16 months for the intermediate-risk group and 6 months for the high-risk group (P=0.004). Median survival was not reached in the low-risk group, while it was 21 months for the intermediate-risk group and 31 months for the high-risk group (P=0.14). Based on these results, we advocate baseline assessment of the EGFR T790M mutation together with expression of DNA-repair status to predict outcome and provide individualized treatment to patients with EGFR activating mutations.

4.3. Rationale for combination therapy with erlotinib and bevacizumab

Bevacizumab is a humanized antibody targeting the vascular endothelial growth factor VEGF, which plays an important role in tumor angiogenesis. The ECOG 4599 and AVAIL trials in patients with metastatic NSCLC demonstrated superior response and survival rates with bevacizumab plus chemotherapy, compared with chemotherapy alone (23, 24). The safety and tolerability of bevacizumab in combination with chemotherapy in patients with NSCLC is well documented in the SAIL and ARIES trials (25, 26). The combination of bevacizumab with erlotinib also has a favorable safetly profile in patients with adenocarcinoma of the lung, precluding patients with tumor bleeding, or with centrally located and cavitating tumors. Several trials have been previously conducted using the combination of bevacizumab and erlotinib in molecularly unselected NSCLC patients (27, 28, 29). The recognition that T790M could represent more than 50% and up to 62% of cases

with clinical progression to erlotinib leads to the development of new treatment approaches to overcome this common mechanism of acquired resistance.

In preclinical models, gefitinib and erlotinib had similar profiles of in vitro activity and caused sustained tumor regressions in vivo in the sensitive HCC827 cell line. In all four resistant cell lines including H1975 (L858R plus T790M), the combination of bevacizumab and erlotinib was significantly more effective than erlotinib alone (30). This model suggests that patients harboring EGFR mutations (del19 or L858R) plus T790M could be sensitive to the addition of bevacizumab to erlotinib. We therefore raise the hypothesis that bevacizumab could prolong the PFS obtained with erlotinib in the subgroup of patients with initial presence of the T790M mutation.

4.4. Circulating DNA

Tumors are shedding DNA into the bloodstream, opening a way for minimally-invasive translational cancer research (31). We and others previously showed that circulating cell-free DNA in the blood of patients with lung cancer can be readily isolated, quantified, and has a prognostic value (32, 33). Moreover, circulating DNA is a source of cancer-specific genetic and epigenetic alterations, including gene mutations and methylation (34, 35, 36, 37). EGFR mutations, including the T790M, have been detected in the circulating DNA in a meaningful number of patients with advanced lung cancer and tumor EGFR mutations (38). The clearance of EGFR mutations in blood could be a molecular marker of response and the reappearance of mutations can herald clinical progression. Although EGFR mutations can be detected in serum as well as plasma, there is a significant percentage of patients where they are found only in serum or only in plasma. To maximise the likelihood of a successful EGFR mutation analysis in blood, the collection of both plasma and serum is essential. Therefore, in the present trial, EGFR mutations in serum and plasma are determined at baseline and at the time of radiographic response assessments to validate test performance and to further study the utility of circulating EGFR mutations to monitor the disease.

4.5. Hypothesis

Our findings prompt us to propose a model of treatment whereby patients with EGFR mutations (single or with T790M) can attain a benefit with longer overall PFS when treated with erlotinib plus bevacizumab. When the patients are grouped by BRCA1 mRNA levels and T790M the hypothesis is that the combination of erlotinib plus bevacizumab can improve the PFS in all subgroups; for example in those with low BRCA1 levels with very long PFS, the addition of bevacizumab can further improve long term outcome, but also in the poor prognostic group of patients with elevated BRCA1 and the concurrent presence of the T790M where, according to our data, the PFS under erlotinib alone is 3 months.

4.6. Further plans

We postulate that patients with the double EGFR mutation harbour two tumour populations; patients with the T790M could display a differential sensitivity to cisplatin based on the levels of BRCA1 expression and therefore, customized chemotherapy based on BRCA1 levels could be indicated in these patients. Hypoxia suppresses homologous recombination repair in human cells via transcriptional downregulation of BRCA1 and RAD51. The downregulation is caused by stimulating E2F4/p130 occupancy of the BRCA1 and RAD51 promoters (39, 40, 41). Intriguingly, PARP inhibitors cause BRCA1 and RAD51 downregulation via induction of E2F4/p130 binding to the BRCA1 and RAD 51 promoters

(42). Future clinical trials will be planned to further develop a customized approach to the targeting of DNA repair in patients with lung cancer.

5. Objectives and endpoints

5.1. Primary objective

To determine progression free survival of patients with advanced non-squamous NSCLC harbouring at diagnosis EGFR mutations with and without T790M mutation, treated with the combination of erlotinib and bevacizumab.

Hypotheses of interest:
When treated with **bevacizumab and erlotinib**

a. Median PFS increases to 18 months for patients with EGFR T790M mutation

b. Median PFS is **approximately 18 months** or more in patients without EGFR T790M mutation.

5.2. Secondary objectives

5.2.1. To evaluate secondary measures of clinical efficacy including overall survival (OS), time to treatment failure (TTF), objective response rate (ORR), disease control rate (DCR) and duration of response (DR).

5.2.2. To assess the safety and the tolerability of the erlotinib and bevacizumab combination.

5.2.3. To evaluate the correlation of BRCA1 mRNA and AEG-1 mRNA expression and T790M with progression-free survival.

5.2.4. To monitor EGFR mutations (including T790M) in serum and plasma longitudinally.

5.2.5. To evaluate molecular biomarkers related to EGFR TKI and bevacizumab.

5.2.6. To determine the feasibility of re-biopsies at the time of progression and gene-expression arrays for decision-making for second-line treatment

5.2.7. To study the feasibility of recommending customized second-line chemotherapy based on BRCA1 and AEG-1 mRNA levels.

5.3. Primary endpoint

Progression-free survival. For definition, see section 14.1

5.4. Secondary endpoints

5.4.1. Overall survival (OS)

5.4.2. Time to treatment failure (TTF)

5.4.3. Objective response (OR)

5.4.4. Adverse events graded according to CTCAE V4.0

5.4.5. Disease control (DC)

5.4.6. Duration of response (DR)

For definitions, see section 14.

6. Trial design, duration and termination

This is a multinational, multi-center trial of erlotinib plus bevacizumab in patients with advanced non-squamous NSCLC harbouring EGFR mutations, including two separate phase II substudies.

Only EGFR mutated patients may enter the study. Approximately 1135 patients with advanced non-small cell lung cancer are expected to be screened to include 102 patients with activating EGFR mutations.

Patients may continue treatment on this trial as long as there is evidence of clinical benefit in the judgment of the investigator. Trial subjects will receive trial medication up to 18 months after the inclusion of the last patient. All patients who are still benefiting from their treatment at that time have to be switched to commercial drug which will be reimbursed by Roche.

Patient accrual is expected to be completed within 12 months including a run-in-period of 3 months. Treatment and follow-up is expected to extend the study duration to a total of 48 months. Patients will be followed until death – thus follow-up estimated up to 3 years following the enrolment of the last patient.

The trial will end with the preparation of the final report, scheduled for month 54 after the inclusion of the first patient.

7. Patient selection

Only patients with a centrally confirmed status of EGFR mutation are eligible. The mutation status may first be assessed locally by a certified laboratory, but for all patients tumor material has to be submitted to the reference laboratory (see section 9) for immediate confirmatory testing.

Written informed consent needs to be obtained prior to shipment of tissue to the central laboratory.

Patients should only be selected and consented for screening if they fulfil the criteria in the next section:

7.1. Inclusion criteria

Patient characteristics

7.1.1. Age ≥ 18 years

7.1.2. ECOG performance status 0-2

7.1.3. Adequate haematological function: haemoglobin > 9 g/dL, neutrophils count $>1.5\times10^9$/L, platelet count > 100×10^9/L

7.1.4. Adequate coagulation: INR ≤ 1.5

7.1.5. Adequate liver function: Total bilirubin < 1.5 × ULN, ALT and/or AST < 2.5 × ULN, alkaline phosphatase < 5 ULN, except in the presence of exclusive bone metastases and in the absence of any liver disorder.

7.1.6. Adequate renal function: Calculated creatinine clearance ≧ 50 mL/min (Cockroft-Gault) and proteinuria < 2+ (dipstick).

7.1.7. Oral swallowing capability, patient capable of proper therapeutic compliance, and accessible for correct follow-up.

7.1.8. Life expectancy of at least 2 months.

7.1.9. Women of childbearing age, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine pregnancy test within 7 days before beginning treatment. Not eligible: Women who are pregnant or in the period of lactation.

7.1.10. All sexually active men and women of childbearing age must use an effective contraceptive method during the study treatment and for a period of at least 12 months following the last administration of trial drugs. Not eligible: sexually active men and women of childbearing age who are not willing to use an effective contraceptive method during the study.

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

a) trial treatment

b) tissue submission for central review and central EGFR testing

Disease characteristics

7.1.12. Pathological diagnosis of predominantly non-squamous, non-small-cell lung cancer (NSCLC). Not eligible: patients with any other lung cancer subtype, patients with mixed NSCLC with predominantly squamous cell cancer, or with any small cell lung cancer (SCLC) component.

7.1.13. TNM version 7 stage IV disease including M1a (malignant effusion) or M1b (distant metastasis), or locally advanced disease not amenable to curative treatment (including patients progressing after radio-chemotherapy for stage III disease). Not eligible: patients who are candidates for radical surgery and/or radio(chemo)therapy with curative intention.

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

7.1.15. Centrally confirmed EGFR exon 19 deletion (del19) or exon 21 mutation (L858R). Not eligible: patients with local test result not confirmed by central laboratory.

Note: if the patient needs immediate treatment, the investigator may register the patient based on locally determined mutation status and start treatment before

confirmation, using trial medication. If the EGFR mutation status is not confirmed by the central reference laboratory, the patient will be taken off trial treatment and will undergo an end-of-treatment assessment. The patient must be followed up per protocol (see section 9).

7.1.16. Patients with asymptomatic and stable cerebral metastases will be eligible for the study. Not eligible: patients with symptomatic or instable cerebral metastases requiring medical treatment.

7.2. Exclusion criteria

Prior/concurrent disease and conditions

7.2.1. Not eligible: patients with increased risk of bleeding, defined by:

- major surgery or significant traumatic injury within 28 days prior to inclusion
- minor surgical procedure within 7 days, or placement of a vascular access device within 2 days of the study enrolment
- history or evidence of bleeding diathesis or hereditary coagulopathy
- history of haemoptysis (defined as at least half a teaspoon's emission of red blood) in the 3 months prior to inclusion)
- evidence by CT of tumor cavitations, or tumours invading or abutting major blood vessels
- Inadequately controlled hypertension (systolic blood pressure > 150 mm Hg and / or diastolic > 100 mm Hg)
- prior history of hypertensive crisis or hypertensive encephalopathy

7.2.2. Not eligible: patients with clinically significant cardiovascular diseases, including

- cerebral vascular accident (<6 months before inclusion)
- acute myocardial infarction (<6 months before inclusion)
- unstable angina
- congestive heart failure class > NYHA II
- serious cardiac arrhythmia requiring medication during the study and which could interfere with regularity of study treatment or is not controlled with medication.

7.2.3. Not eligible: patients with a history of thrombosis or thromboembolism in the 6 months prior to treatment

7.2.4. Not eligible: patients with gastrointestinal problems including

- intestinal transit problems (such as malabsorption syndrome, chronic intestinal inflammatory disease, or other pathologies that can alter absorption of the medication
- history of abdominal fistula, intestinal perforation or intra-abdominal abscess within 6 months prior to inclusion
- uncontrolled active peptic ulcer

- presence of trachea-oesophageal fistula.

7.2.5. Not eligible: patients with neurologic problems, including

- evidence of spinal cord compression
- significant neurological or psychiatric disorders (including dementia and epileptic seizures).

7.2.6. Not eligible: Patients who have had in the past 5 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 breast carcinoma.

7.2.7. Not eligible: patients with any known significant ophthalmologic anomaly of the ocular surface. The use of contact lenses is not recommended.

7.2.8. Not eligible: patients 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 study.

7.2.9. Not eligible: Known hypersensitivity to bevacizumab or erlotinib or any of its excipients.

Prior, recent or concurrent treatment

7.2.10. Not eligible: patients who received prior chemotherapy for metastatic disease. Patients with prior neoadjuvant or adjuvant chemotherapy or definitive radio-chemotherapy for localised disease are eligible if chemotherapy has stopped at least 6 months before entering the study

7.2.11. Not eligible: patients who received previous treatment for lung cancer with drugs targeting EGFR or VEGF. Patients with previous intraocular treatment with VEGF -targeting drugs are eligible.

7.2.12. Not eligible: patients who received treatment with an investigational drug agent during the 3 weeks before enrolment in the study.

7.2.13. Not eligible: patients with current or recent use (within the last 10 days) of full doses of anticoagulants or thrombolytics, either orally or parenterally. Use of anticoagulant prophylaxis is permitted (low dose heparin or aspirin <=325 mg, prophylactic FXa inhibitors).

7.2.14. Not eligible: patients with concurrent use of CYP3A4 inducers/inhibitors (such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, or grapefruit or grapefruit juice).

8. Patient screening and registration

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

8.1. Enrolment of patient

Complete the following steps to enroll a patient on this trial. Please consult the ***BELIEF Procedures Manual*** for detailed instructions.

Note that written informed consent has to be obtained from the patient prior to any trial-specific intervention including submission of tissue for central EGFR testing.

8.1.1. Screening: Verify eligibility (including presence of EGFR mutation if done locally) and register the patient in the RDE facility. The date the Informed Consent Form and the consent to pathology material submission section of the Informed Consent Form were signed by the patient and the date signed by the investigator are both required to complete the eligibility checklist.

8.1.2. If EGFR mutation testing is to be done nationally (see section 9), submit tissue material to national laboratory for evaluation of EGFR mutation status. Enter EGFR mutation status in RDE facility once result has been communicated by national laboratory.

8.1.3. The laboratory which has done the EGFR mutation testing (local lab or national lab) submits tissue material to central reference laboratory for central evaluation of EGFR mutation status (see section 9). The enrolling site must confirm shipment in the RDE system.

8.1.4. Enrolment: Within 48 hours of receipt of the tissue material, the central reference laboratory will inform the site (e-mail from RDE system) if the material is sufficient and usable for EGFR mutation analysis and T790M determination or not. If the material is accepted this will trigger the enrolment into the trial and the trial treatment can start.

Note: if the patient needs immediate treatment, the investigator may enroll the patient immediately (confirmation of the trial chair required, see ***BELIEF Procedures Manual*** for detailed instructions) and start treatment before acceptance of tissue by the central Lab, using trial medication. Tissue material for central mutation testing has to be submitted as soon as possible but no more than 10 working days after the eligibility override.

If the tissue quality and/or quantity is not accepted by the central reference laboratory a second sample has to be sent to the central Lab within 10 days after awareness that the samples has been rejected. If the second sample is also not accepted, no second sample can be sent or the EGFR mutation status is not confirmed, the patient will be taken off trial treatment and undergo an end-of-treatment assessment. The patient must be followed up per protocol.

9. Central testing of EGFR mutation status

Only patients with centrally confirmed EGFR exon 19 deletion (del19) or exon 21 mutation (L858R) are eligible. There are three options for the determination of mutation status:

1. The mutation status may be assessed locally by a certified laboratory, but must be confirmed by the central reference laboratory.
2. The mutation status may be assessed nationally by a certified laboratory, but must be confirmed by the central reference laboratory.

If the EGFR mutation status is not confirmed by the central reference laboratory, the patient will be taken off trial treatment and will undergo an end-of-treatment assessment. Such a patient must be followed up per protocol.

3. Tumour material can also be submitted directly to the central reference laboratory for immediate testing without prior local testing.

9.1. Location of central reference laboratory

The central reference laboratory is

Laboratory of Oncology
Pangaea Biotech SA
USP Dexeus Institute
Calle Sabino Arana 5-9
08028-Barcelona, Spain
http://www.pangaeabiotech.com/

If the EGFR mutation status is not confirmed by the central reference laboratory, or the submitted FFPE material is found to be not sufficient and usable for EGFR mutation analysis and T790M determination, the patient will be taken off trial treatment and will undergo an end-of-treatment assessment. The patient must be followed up per protocol.

9.2. Shipping of samples to central laboratory

Once the patient has consented to the participation, send a formalin fixed, paraffin embedded block or alternatively at least 5 sections mounted on penmembrane slides from tumour biopsy, original surgery or cell block to the central laboratory (national reference laboratory or the central reference laboratory) for EGFR mutation analysis (consult the Group/Country specific instructions for your country). Please send the tissue with a Haematoxylin/Eosin slide together with the original report of the mutation analysis (if applicable) and the Pathology report to the central laboratory. Please consult the ***BELIEF Procedures Manual*** for detailed instructions.

9.3. Communication of result

The central reference laboratory (Pangaea Biotech) will communicate within 48 hours of receipt of the material if the submitted FFPE material is sufficient and usable for EGFR mutation analysis and T790M determination. This confirmation triggers the enrollment of the patient into the study and trial treatment can start (exception see note in section 8.1).

The results of the mutation testing will be communicated within 7 working days; if this is not feasible in exceptional cases, the submitting site will be contacted within 7 days to explain the reasons.

10. Study drug

Erlotinib and bevacizumab are the investigational drugs used in this trial. Both will be provided by Hoffmann-La Roche.

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

11. Trial treatments

Drug therapy is to begin within 7 days of enrolment

11.1. Sequence of treatments

Patients will be treated with erlotinib and bevacizumab.

Bevacizumab: 15 mg/kg i.v. on day 1 of each 3-week cycle (+/- 3 days)

Erlotinib: 150 mg p.o., daily

11.2. Dosage, administration and compliance

11.2.1. Bevacizumab dose / route / regimen

The dose of bevacizumab is calculated based on the body weight of the patient [kg]. If the body weight changes by 10% or more in the course of the treatment, dose adjustment is recommended for further infusions. If the body weight changes by less than 10%, no dose adjustment is needed.

Blood pressure should be routinely measured before every infusion and after a resting period of 10 min.

Proteinuria should be routinely measured before every infusion of bevacizumab using dipstick.

No routine premedication (e.g. to prevent infusion reaction) is recommended for bevacizumab.

The initial infusion of bevacizumab should be given over 90 minutes. If the initial infusion is well tolerated, the second infusion can be given over 60 minutes. If the second infusion is again well tolerated, all subsequent infusions can be given over 30 minutes.

In case of relevant toxicity, bevacizumab should be paused or discontinued. Dose reductions are not recommended.

Bevacizumab should be given every 3 weeks +/- 3 days. If the administration was pre- or postponed the patient should (if possible) return to schedule and the next dose should be given 21 days after the planned last administration.

11.2.2. Erlotinib dose / route / regimen / compliance

Erlotinib is started at a fixed dose of 150 mg per day.

Tablets should be taken at a fixed time each day and at least 1 hour before or 2 hours after the ingestion of food. Treatment compliance for erlotinib will be monitored by a patient diary. Patients will be asked to record the time and date they take each dose in the diary. They will be instructed to bring it to each study visit for assessment of compliance. Patients will also be instructed to bring all unused erlotinib tablets to each study visit. Please refer to the ***Procedures Manual*** for details. No routine premedication (e.g. to prevent skin toxicity) is recommended for erlotinib.

Smokers have reduced plasma levels and should be counselled for smoking reduction or cessation, the dose of 150 mg must never be increased.

In case of relevant toxicity, dose reductions are recommended to improve the tolerance.

11.3. Precautions

Women with childbearing potential and sexually active men must use effective contraception during the trial and 12 months thereafter.

11.4. Concomitant treatment

The following treatments are **allowed** during the treatment phase of the trial:

- Approved drugs for other medical indications than cancer including low dose heparin or aspirin (≤ 325 mg per day) and FXa inhibitors, except full anticoagulation (see section below)
- Palliative and supportive care, including analgesic radiotherapy
- Safe alternative medicine if potential interactions with trial drugs can be excluded.

The following treatments are **NOT allowed**:

- Investigational or approved anticancer drugs, including chemotherapy, immunotherapy, and hormonal anti-cancer therapy
- Full-dose oral, intravenous or subcutaneous anticoagulants, asasantin or clopidogrel
- Medications, herbal extracts or food which can interact with erlotinib (CYP3A4 inducers/inhibitors such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, or grapefruit or grapefruit juice).

11.5. Treatment delay and dose modification for toxicity

In case of toxicity, symptomatic treatment and dose interruptions should be used according to the following sections. Repeated dose interruptions are allowed as required, for a maximum of 6 weeks on each occasion (a delay of a maximum of 6 weeks after the planned drug administration is allowed). **As long as at least one of the study drugs can be continued, the patient remains on trial treatment.** In case of doubt please contact immediately one of the trial chairpersons.

If one of the trial drugs is stopped for a reason other than unacceptable toxicity, the case needs to be discussed immediately with the trial chair or one of the trial coordinators to clarify if the patient can remain on study medication with the other drug.

11.5.1. Bevacizumab

There are no recommended dose reductions.

Temporarily suspend bevacizumab for:

- At least 4 weeks prior to elective surgery
- First venous thromboembolic event grade 3 or 4 requiring full anticoagulation; bevacizumab may be resumed after initiation of therapeutic-dose anticoagulant therapy if the patient is on a stable dose of anticoagulant
- Severe hypertension not controlled with medical management. Blood pressure should be less than 150 mmHg systolic and 100 mmHg diastolic before bevacizumab is given. If blood pressure is higher, measurement should be repeated

and if hypertension is confirmed, antihypertensive medication should be started and bevacizumab should be delayed until blood pressure drops below 150/100mmHg.

- Proteinuria Grade 3; resume bevacizumab once grade 2 or less has been attained.
- Grade 3 or 4 bevacizumab-related events occurring for the first time: bevacizumab should be discontinued until toxicity improves to grade 1. When a grade 3 o 4 occurs for second time, bevacizumab should be discontinued permanently

Discontinue bevacizumab for:

- Arterial thromboembolism (any grade)
- Febrile grade 4 neutropenia and/or grade 4 thrombocytopenia regardless of the relationship to treatment
- Grade ≥ 3 venous thrombosis/embolism (including pulmonary embolism) and recurrent venous thromboembolic event requiring full anticoagulation
- Gastrointestinal perforations (gastric ulcer, fistula formation in the gastrointestinal tract, intra-abdominal abscess)
- Grade ≥ 2 fistula formation involving an internal organ
- Cerebral or cardiac ischemic events
- Grade ≥ 3 left ventricular dysfunction (CHF)

- Wound dehiscence and wound healing complications requiring medical intervention
- Nephrotic syndrome.
- CNS bleeding (any grade) or ≥ grade 3 bleeding of any kind
- Medically significant hypertension not controlled with antihypertensive therapy, hypertensive crisis or hypertensive encephalopathyPosterior reversible encephalopathy syndrome (PRES), previously called Reversible posterior leukoencephalopathy syndrome (RPLS)
- Severe infusion reactions
- Recurring grade 3 or 4 bevacizumab-related event
- A treatment delay of more than 6 weeks

11.5.2. Erlotinib

Temporarily suspend erlotinib:

- In patients who develop an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough or fever, treatment with erlotinib should be interrupted pending diagnostic evaluation.
- in patients with dehydration who are at risk for renal failure
- in patients with severe bullous, blistering or exfoliative skin conditions
- in patients with acute or worsening ocular disorders

- in patients with severe changes in liver function such as doubling of total bilirubin and/or tripling of transaminases, especially in the setting of baseline values outside normal range
- in patients with total bilirubin >3 x ULN and/or transaminases >5 x ULN. Patients with hepatic impairment should be closely monitored during therapy.

Permanently discontinue erlotinib for:

- Interstitial Lung Disease (ILD)
- hepatic failure
- gastrointestinal perforation
- A treatment delay of more than 6 weeks

Dose reductions

When dose reduction is necessary, the erlotinib dose should be reduced in 50 mg decrements.

- Diarrhea can usually be managed with loperamide. Patients with severe diarrhea who are unresponsive to loperamide or who become dehydrated may require dose reduction or temporary interruption of therapy. Patients with severe skin reactions may also require dose reduction or temporary interruption of therapy.
- In the setting of worsening liver function tests, before they become severe, dose reduction with frequent liver function test monitoring should be considered.
- For other erlotinib-related adverse events greater than or equal to grade 3, erlotinib should be dose reduced or delayed until resolution to grade 0-1. If not resolved within 4 weeks, erlotinib must be permanently discontinued. If resolved to grade 0-1, the lower dose can be maintained or again increased to 150 mg maximum. On second occurrence of grade 3-4 events, erlotinib should be permanently discontinued.

11.6. Treatment duration

Patients remain on treatment until one of the following events:

- Documented progression according to RECIST v1.1
- Unacceptable toxicity
- Any interruption of both of the study drugs for more than 6 weeks. Patients who discontinue only one of the study drugs and continue with the other drug are considered to remain on the trial treatment.

  If one of the trial drugs is stopped for a reason other than unacceptable toxicity, the case needs to be discussed immediately with the trial chair or one of the trial coordinators to clarify if the patient can remain on study medication with the other drug.
- Medical condition that prevents further treatment
- Significant protocol violation
- Patient withdraws consent

- Patient becomes pregnant

If only one of the two trial drugs has to be stopped and the other drug can be continued, the patient remains on the trial. If both drugs have been stopped for any reason, the patient enters the follow-up phase of the trial. **Up to the time of confirmation of disease progression, the schedule of evaluations has to be kept as if the patient were still receiving treatment**. Patients who discontinue trial treatment should be assessed by the investigator who must document the case on the appropriate CRF. Leftover erlotinib tablets should be returned by the patient.

Trial subjects will receive trial medication up to 18 months after the inclusion of the last patient. All patients who are still benefiting from their treatment at that time have to be switched to commercial drug which will be reimbursed by Roche.

12. Safety of investigational products

12.1. Bevacizumab

12.1.1. Known adverse reactions

The following NCI CTC grade 3 to 5 adverse reactions have been reported:

Very common (≥ 10%): Febrile neutropenia, Leucopenia, Thrombocytopenia, Neutropenia, Peripheral sensory neuropathy, Hypertension, Diarrhoea, Nausea, Vomiting, Asthenia, Fatigue

Common (1 – <10%): Sepsis, Abscess, Infection, Anaemia, Dehydration, Cerebrovascular accident, Syncope, Somnolence, Headache, Cardiac failure congestive, Supraventricular tachycardia, Arterial Thromboembolism (pooled arterial thromboembolic events including cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic adverse reactions), Deep vein thrombosis, Haemorrhage, Pulmonary embolism, Dyspnoea, Hypoxia, Epistaxis, Intestinal Perforation, Ileus, Intestinal obstruction, Abdominal pain, Gastrointestinal disorder, Stomatitis, Palmar-plantar erythrodysaesthesia syndrome, Muscular weakness, Myalgia, Arthralgia, Proteinuria, Urinary Tract Infection, Pain, Lethargy, Mucosal inflammation.

12.1.2. Contraindications

Bevacizumab is contraindicated in patients with known hypersensitivity to any components of the product, and to chinese hamster ovary cell products or other recombinant human or humanised antibodies.

12.1.3. Gastrointestinal Perforations

Patients may be at increased risk for the development of gastrointestinal perforation when treated with bevacizumab. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation.

Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or non-squamous non-small cell lung cancer, up to 2.0% in patients with metastatic renal cell cancer, newly diagnosed glioblastoma, and in patients with ovarian cancer receiving front-line treatment, and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. Cases of GI perforations have also been observed in patients with relapsed

glioblastoma. Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2%-1% of all bevacizumab treated patients.

The presentation of these events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis, or chemotherapy-associated colitis.

12.1.4. Fistulae

Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Patients may be at increased risk for the development of fistulae when treated with bevacizumab. Permanently discontinue bevacizumab in patients with tracheoesophageal (TE) fistulae or any Grade 4 fistulae.

In Bevacizumab clinical trials, gastrointestinal fistulae have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancer. Uncommon (≥0.1% to <1%) reports of other types of fistulae that involve areas of the body other than the gastrointestinal tract (e.g. bronchopleural, urogenital, biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistulae not arising in the GI tract, discontinuation of bevacizumab should be considered.

12.1.5. Haemorrhage

Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour associated haemorrhage. Bevacizumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during bevacizumab therapy.

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 6.5% in bevacizumab-treated patients, compared to 0 to 2.9% of patients in the chemotherapy control group. The haemorrhagic events that have been observed in Bevacizumab clinical studies were predominantly tumour-associated haemorrhage and minor mucocutaneous haemorrhage (e.g. epistaxis).

Gastrointestinal haemorrhages, including rectal bleeding and melaena have been reported in colorectal patients, and have been assessed as tumour-associated haemorrhages.

Tumour-associated haemorrhages were also seen rarely in other tumour types and locations and included cases of central nervous system (CNS) bleeding in patients with CNS metastases and in patients with glioblastoma.

Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patient has not been prospectively evaluated in randomised clinical studies. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in case of intracranial bleeding.

Across all Bevacizumab clinical trials, mucocutaneous haemorrhages were seen in up to 50% of patients treated with Avastin. These were most commonly NCI-CTC Grade 1

epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any change in the Bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent.

There have also been less common events of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding or vaginal bleeding.

There is no information on the safety profile of bevacizumab in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. However, patients who developed venous thrombosis while receiving bevacizumab therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with full dose of warfarin and bevacizumab concomitantly. Nevertheless, bevacizumab should be discontinued in the event of venous or arterial thromboembolism requiring full anticoagulation.

12.1.6. Pulmonary Haemorrhage / Haemoptysis

Patients with non–small cell lung cancer treated with bevacizumab may be at risk for serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/haemoptysis (>2.5 ml red blood) should not be treated with bevacizumab. Bevacizumab should be discontinued in the event of significant haemorrhage.

Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in studies in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, Bevacizumab therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were Bevacizumab therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent studies, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominant squamous histology, all Grade events were seen with a frequency of up to 9% when treated with Bevacizumab plus chemotherapy compared with 5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with Bevacizumab plus chemotherapy as compared with <1% with chemotherapy alone. Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome

12.1.7. Hypertension

An increased incidence of hypertension (all grades) of up to 42.1% was observed in patients treated with bevacizumab compared with up to 14% in the comparator arm. In clinical trials across all indications the overall incidence of NCI-CTC Grade 3 and 4 hypertension in patients receiving Bevacizumab ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with Avastin compared to up to 0.2% patients treated with the same chemotherapy alone.

Clinical safety data suggest that the incidence of hypertension is likely to be dose dependent. Pre existing hypertension should be adequately controlled before starting

bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Monitoring of blood pressure is recommended during bevacizumab therapy.

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if, the patient develops hypertensive crisis or hypertensive encephalopathy.

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal. The risk of Bevacizumab-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

12.1.8. Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES), a rare neurological disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. Symptoms usually resolve or improve within days, although some patients have experienced neurologic sequelae. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known.

12.1.9. Arterial Thromboembolism

In clinical trials, the incidence of arterial thromboembolism adverse reactions including cerebrovascular accidents, transient ischaemic attack (TIA) and myocardial infarction (MI) was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone.

In clinical trials, the overall incidence ranged up to 5.0% in the Bevacizumab containing arms compared up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving Bevacizumab in combination with chemotherapy compared to 0.5% of patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischemic attacks) were reported in up to 2.3% of Avastin treated patients versus 0.5% of patients in the control group: myocardial infarction was reported in 1.4% of Avastin treated versus 0.7% of patients in the observed control group.

Patients receiving Avastin plus chemotherapy with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic events during Avastin therapy. Caution should be taken when treating such patients with Avastin

Bevacizumab should be permanently discontinued in patients who develop arterial thromboembolic reactions.

12.1.10. Venous Thromboembolism

In clinical trials across indications, the overall incidence of venous thromboembolic events ranged from 2.8% to 17.3% in the Avastin containing arms compared to 3.2% to 15.6% in

the chemotherapy control arms. Venous thromboembolic events include deep venous thrombosis and pulmonary embolism.

Grade 3-5 venous thromboembolic events have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab compared with up to 4.9% in patients with chemotherapy alone. Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive Avastin in combination with chemotherapy versus chemotherapy alone.

Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under bevacizumab treatment. Bevacizumab should be discontinued in patients with pulmonary embolism.

12.1.11. Congestive Heart Failure

Reactions consistent with congestive heart failure (CHF) were reported in clinical trials. The symptoms ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Most of the patients who experienced CHF had metastatic breast cancer (mBC) and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

Most patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of Avastin, patients with pre-existing CHF of NYHA II – IV were excluded, therefore, no information is available on the risk of CHF in this population.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, concomitant cardiotoxic therapy or congestive heart failure with bevacizumab.

12.1.12. Neutropenia and infections

Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

12.1.13. Wound Healing complications

Bevacizumab may adversely affect the wound healing process. Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. Bevacizumab therapy should be withheld 4 weeks prior to elective surgery.

Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

12.1.14. Proteinuria

In clinical trials, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone.

Grade 4 proteinuria (nephrotic syndrome) was uncommon in patients with Avastin. In the event of Grade 4 proteinuria Avastin treatment should be permanently discontinued.

Proteinuria should be measured before every infusion of bevacizumab using dipstick. If proteinuria is CTCAE grade 0-2, bevacizumab can be given. If proteinuria is CTCAE grade 3, delay bevacizumab and resume only if grade 2 or less has been attained. If proteinuria does not resolve, permanently discontinue bevacizumab.

12.1.15. Hypersensitivity reactions, infusion reactions

Patients may be at risk of developing infusion / hypersensitivity reactions. Routine premedication is not recommended. However, close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered.

12.1.16. Osteonecrosis of the jaw (ONJ)

The overall incidence of ONJ in bevacizumab-treated patients is estimated to be less than 1 in 10,000. The incidence of ONJ in patients with cancer treated with high doses of intravenous bisphosphonates has been estimated to be in the range of 1-10 per 100 patients.

Of 55 cases, 43 were confounded by concomitant chemotherapy, with concomitant bisphosphonate use described in 31 cases (56%). The most frequently used bisphosphonate was zoledronic acid which is known to be associated with ONJ. In another 12 cases, underlying medical conditions such as surgery, trauma, dental extraction, radiotherapy etc. provide alternative explanations of the reported event.

There are multiple risk factors for the development of ONJ in cancer treated patients, and the role of bevacizumab in exacerbating these risk factors is uncertain. A causative role of bevacizumab in ONJ is uncertain, and cannot be established.

12.1.17. Ovarian failure/fertility

Bevacizumab may impair female fertility. Therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Avastin.

Elderly Patients:
In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient ischemic attacks and myocardial infarction as compared to those aged ≤65 years when treated with Bevacizumab. Other reactions with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia, thrombocytopenia; and all Grade neutropenia, diarrhoea, nausea, headache and fatigue.

No increase in the incidences of other reactions, including gastrointestinal perforation, wound healing complications, hypertension, proteinuria, congestive heart failure and haemorrhage, was observed in elderly patients (> 65 years) receiving Avastin as compared to those aged ≤ 65 years treated with Avastin.

12.2. Erlotinib

12.2.1. Known adverse reactions

The most common adverse reactions (>20%) in patients with non-small cell lung cancer are rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, infection and vomiting.

12.2.2. Interstitial Lung Disease (ILD)

There have been infrequent reports of serious ILD-like events (including fatalities) in patients receiving erlotinib for the treatment of NSCLC, pancreatic cancer, or other advanced solid tumours. In the single-agent study in patients with NSCLC, Study BR.21, the incidence of serious ILD-like events (0.8%) was the same in the placebo and erlotinib groups. No imbalance was noted in the incidence of serious ILD-like events in the 2 large first-line NSCLC studies (Studies OSI2298g and BO16411), which utilized a standard platinum-based regimen with or without erlotinib. In the combination study with gemcitabine in patients with pancreatic cancer, Study PA.3, the incidence of ILD-like events was 2.5% versus 0.4% in the erlotinib plus gemcitabine versus the placebo plus gemcitabine groups, respectively. The overall incidence of ILD-like events in approximately 32,000 erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 1.1%. When cases from a postmarketing surveillance study from Japan are excluded (N = 5860; 3.4% incidence), the incidence from rest of world was approximately 0.6%. Some examples of reported diagnoses included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, alveolitis, and lung infiltration. Most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

In the event of acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever, erlotinib therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued and appropriate treatment instituted as necessary, including corticosteroids.

12.2.3. Diarrhea

Diarrhea (sometimes severe) has occurred in patients receiving erlotinib and was usually managed by loperamide; however, reduction in the dose of erlotinib was occasionally necessary. In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, erlotinib therapy should be interrupted and appropriate measures should be taken to intensively treat the dehydration. Since there have been rare reports of hypokalemia and/or acute renal failure (including fatalities), secondary to severe dehydration, renal function and serum electrolytes (including potassium) should be monitored in this setting.

12.2.4. Gastrointestinal Perforation

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

12.2.5. Renal Failure

Rare cases of acute renal failure or renal insufficiency have been reported (including fatalities). Many of these cases have been associated with significant dehydration due to diarrhea, vomiting, and/or anorexia. Other possible contributing factors have included concomitant medications and/or chemotherapy, pre-existing renal disease, or other medical conditions associated with renal disease. Periodic monitoring of renal function in patients with these risk factors is recommended.

12.2.6. Myocardial Infarction/Cerebral Vascular Accident

In the pancreatic cancer Study PA.3, small numerical imbalances in the incidence of stroke and myocardial infarction (including fatalities) were noted in patients receiving erlotinib in combination with gemcitabine. A causal relationship to erlotinib has not been established.

12.2.7. Hepatotoxicity

Liver function abnormalities, including elevated serum ALT, AST, and/or bilirubin, have been observed infrequently with single-agent erlotinib and occasionally with erlotinib in combination with concomitant chemotherapy, e.g. gemcitabine. Rare cases of hepatic failure (including fatalities) have been reported during postmarketing use of erlotinib. Confounding factors for severe hepatic dysfunction have included pre-existing liver disease such as cirrhosis, viral hepatitis, hepatocellular carcinoma, hepatic metastases, or concomitant treatment with potentially hepatotoxic drugs. Periodic monitoring of liver function is recommended. Erlotinib dosing should be interrupted if changes in liver function are severe.

12.2.8. Patients with Hepatic Impairment

In a pharmacokinetic study (Study OSI-774-104) in patients with moderate hepatic impairment (Child-Pugh B) associated with significant liver tumour burden, 10 of 15 patients died on treatment or within 30 days of the last erlotinib dose. One patient died from hepatorenal syndrome, 1 patient died from rapidly progressing liver failure and the remaining 8 patients died from progressive disease. Six of the 10 patients who died had baseline total bilirubin > 3 x ULN suggesting severe hepatic impairment. None of the deaths were considered to be related to erlotinib treatment by the investigators. However, treatment with erlotinib should be used with extra caution in patients with total bilirubin > 3 x ULN. Patients with hepatic impairment (total bilirubin > ULN or Child-Pugh B or C) should be closely monitored during therapy with erlotinib. Erlotinib dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range.

12.2.9. Thrombotic Microangiopathy/Microangiopathic Haemolytic Anaemia with Thrombocytopenia/Haemolytic Uremic Syndrome

Isolated reports of microangiopathic haemolytic anaemia with thrombocytopenia and haemolytic uremia syndrome (HUS) have been received. All patients received erlotinib and gemcitabine concurrently. A causal relationship to erlotinib has not been established.

12.2.10. Bullous and Exfoliative Skin Disorders

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

12.2.11. Ocular Disorders

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

Infrequent occurrences of keratitis have been observed during erlotinib treatment. Isolated reports of uveitis and orbital cellulitis have been reported in patients receiving erlotinib therapy.

Patients who develop irregular or excessive eyelash growth should be monitored for eye symptoms such as eye pain. Careful removal of in-growing/abnormal/elongated eyelashes should be considered if increased growth leads to scratching and/or irritation of the cornea. Patients with a prior history of ocular disorders or additional identifiable risk factors should be closely monitored by a physician.

13. Adverse events and reporting

13.1. 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, see Appendix 3 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

An adverse event is defined as any untoward medical occurrence that occurs from the first dose of study medication until 30 days after the final dose, regardless of whether it is considered related to a medication.

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) 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 study 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 will continue to be followed up during treatment.
- Laboratory abnormalities for non-safety parameters will be documented on the form AE from grade ≥ 3 only
- AEs should not be reported in a narrative description.

13.2. Definition of Serious Adverse Event (SAE)

13.2.1. SAEs during trial treatment

An SAE is defined in general as any undesirable medical occurrence/adverse drug experience that occurs during or within 30 days after stopping study treatment that, at any dose, results in any of the following:

- is fatal (any cause)
- life-threatening,
- requires or prolongs inpatient hospitalization,
- results in persistent or significant disability/incapacity
- is a congenital anomaly or birth defect
- is a secondary malignancy
- requires significant medical intervention

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 jeopardize the patient are also considered serious adverse events.

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 hospitalizations occurring under the following circumstances:

- elective surgery;
- occur on an outpatient basis and do not result in admission (hospitalization < 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).

13.2.2. SAEs after end of trial treatment

During the follow-up phase (starting 30 days after end of trial treatment), 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
- Pregnancy

In the case of pregnancy occurring during the course of the trial 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.

13.3. Definition of Serious Adverse Drug Reaction (SADR)

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

13.4. 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.

13.5. Definition of Adverse Events of Special Interest (AESI)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Products by either Roche or a Regulatory Authority.

The following adverse events are of special interest and must be documented if observed. AESI as specified below must be documented and reported by submitting the completed SAE Report Tab (initial and follow-up) in the RDE system within 10 days after knowledge of the event (Indicate in "Description" section if "non-serious adverse event of special interest" yes or no).

- Interstitial lung disease (ILD)-like events
- Haemorrhage (> or equal to grade 3), with a focus on haemoptysis (> or equal to grade 2) and CNS bleeding (> or equal to grade 2)
- Hypertension

  Patients should be monitored for the development of new hypertension or worsening of a pre-existing hypertension by frequent measurements of blood pressure and should be handled as follows:

  G1: Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg): record as AE, (continue bevacizumab)

G2: Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (≥ 24 hrs); symptomatic increase by > 20 mm Hg (diastolic) or to > 140/90 mm Hg if previously within normal limits; monotherapy indicated
Record as AE and on SAE tab indicate in Description section "non-serious adverse event of special interest": yes
G3 hypertension**:** Stage 2 hypertension (systolic BP >= 160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated,
Record as AE and on SAE tab indicate in Description section "non-serious adverse event of special interest": yes/no (according to seriousness)
> G3 hypertension**:** record as AE and always report as SAE.

- Proteinuria

  G1: Record as AE
  G2 (2+ (dipstick): 1.0-3.4g/24hrs): Record as AE and on SAE tab indicate in Description section "non-serious adverse event of special interest": yes
  (Assess 24-hour-urine before each scheduled dose until ≤ 1g/24hrs).
  G3 proteinuria: Record as AE and on SAE tab indicate in Description section "non-serious adverse event of special interest": yes/no (according to seriousness)
  (Assess 24-hour-urine before each scheduled dose until ≤ 1g/24hrs).

- Arterial (any grade)/venous (> or equal to grade 3) thromboembolic events
- Wound healing complications (> or equal to grade 3)
- Congestive heart failure (> or equal to grade 3)
- Fistulae (non GI or abscess > or equal to grade 2)
- Gastrointestinal perforations, abscesses and fistulae (any grade)
- Reversible posterior leucoencephalopathy syndrome (any grade)

13.6. Reporting SAEs/AESI

Any SAE must be reported by submitting the completed SAE Initial Report Tab in the RDE system within 24 hours of first knowledge of the event (= date of awareness).

Any AESI must be reported by submitting the completed SAE Initial Report Tab in the RDE system within 10 days after first knowledge of the event (= date of awareness).

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

+41 31 389 92 29

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

In case of SAE/AESI submission by fax, the originals of the SAE forms (both initial and follow-up report) will be collected by the monitor. The centres keep a copy for their own records.

The ETOP Safety Office will forward each SAE/AESI to the trial chairs and to Roche and notify principal investigators of any SADR 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 local SAEs.

The ETOP Safety Office will inform Roche and other appropriate persons about all SAEs/AESIs 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/AESI and prepare a summary report of all SAEs received at the end of each month. Principal Investigators will receive the summary report on a monthly basis.

14. Endpoints definition

14.1. Progression-free survival

This is the primary endpoint. It is defined as the time from the date of enrolment until documented progression or death, whichever occurs first.

14.2. Time to treatment failure

Defined as time from the date of enrolment to discontinuation of treatment for any reason (including progression of disease, treatment toxicity, refusal and death).

14.3. Overall survival

Defined as time from the date of enrolment until death from any cause.

14.4. Objective response

Objective response is defined as best overall response (CR or PR) across all assessment time-points according to RECIST Criteria 1.1 (see Appendix 2), during the period from enrolment to termination of trial treatment.

14.5. Disease control

Disease control is defined as achieving

- objective response
- or stable disease for at least 6 weeks

14.6. Duration of response

Defined as interval from the date of first documentation of objective response by RECIST to the date of first documented progression or relapse.

14.7. Toxicity

Adverse events classified according to NCI CTCAE version 4.

15. Biological material and translational research

15.1. Mandatory evaluations

15.1.1. Central pathology review

The work of the pathologist is basic to the success of all studies. Each participating site should identify a pathologist responsible for trial patients. The pathologist determines the diagnosis of non-squamous NSCLC in the biopsy and/or primary resection specimen. The central review pathologist will review the submitted specimens and complete the central pathology review.

Central pathology review reports will be available to institution pathologists who wish to see them. Central pathology review will include histopathological parameters (tumour type and grade). The blocks will be available for prospective and retrospective studies approved by ETOP.

Central review for all patients will take place at

Pangaea Biotech SA
USP Dexeus Institute
Calle Sabino Arana 5-9
08028-Barcelona, Spain

Objectives:

- Central pathology review
- Central EGFR mutation testing for all pts
- Banking of tumour material for future, not yet specified research

15.1.2. Central EGFR testing

EGFR mutation status will be determined at the local sites in most cases. For these cases, the reference laboratory will do a central determination. The results will be communicated to sites.

Procedures for central EGFR testing:

- EGFR sensitive mutations will be run according to Pangaea Biotech's ISO15189 (DNA sequencing for both exon 19 deletions and exon 21 L858R, plus GeneScan for Exon 19 and TaqMan for Exon 21-L858R).
- T790M will be analyzed using a PNA probe plus TaqMan assay.
- BRCA1/AEG1 analysis will be performed in RNA isolated from laser capture microdissected tumour tissue and quantified using relative expression by Real Time Quantitative PCR. Note that BRCA1 analysis in tumour tissues will also be performed according to Pangaea Biotech's accreditation (ISO15189)

Certified laboratory:

Pangaea Biotech SA
USP Dexeus Institute
Calle Sabino Arana 5-9
08028-Barcelona, Spain

With the support of:

Molecular Biology Laboratory
Medical Oncology Service
Hospital Germans Trias i Pujol
Catalan Institute of Oncology
Ctra Canyet, s/n
Badalona, Spain
Rafael Rosell (rrosell@iconcologia.net)
Miguel Angel Molina (mamolina@pangaeabiotech.com)

15.2. Optional evaluations

15.2.1. BRCA1 and AEG-1

BRCA1 mRNA expression and AEG-1 will be determined on FFPE material (only approx. 60% of patients will have enough tumour tissue for BRCA1/AEG-1 analysis).

15.2.2. Biomarker monitoring on serum and plasma samples

Serum and plasma samples are required for biomarker monitoring and to detect molecular alterations corresponding to the tissue.

15.3. Submission of material

The tissue and blood samples collected during the conduct of the trial must be marked with the patient identifier issued by the RDE system and shipped to the central reference laboratory (Pangaea Biotech) and will be stored there for an unlimited time. This precious material will be used for central quality assurance and made available for translational research projects.

15.3.1. Submission of FFPE material

The following items should be submitted for all patients:

1. Pathology Report from primary surgery, if applicable
2. Tumour block from primary surgery, if applicable
3. Pathology Report from diagnosis of advanced / metastatic disease, if available
4. Tumour or cell block from advanced / metastatic disease, if available

Recommended, but not required:

5. Tumour or cell block and pathology report from re-biopsy at progression

As an alternative to the submission of a complete block, at least 5 sections from the block mounted on penmembrane slides are acceptable.

Paraffin-embedded cell blocks produced from malignant effusion are a valuable alternative to tumor blocks. Cytology smears alone are not accepted in this trial.

There is no limitation regarding the age of the tumor sample in this trial. However, recent samples are preferred and investigators should consider a new biopsy in patients relapsing after surgery.

The tissue blocks may be returned to the site upon request after four 1mm cores have been taken for preparing tissue micro-arrays (TMAs).

All reports, slides, and blocks must be marked with the identification number issued by the RDE system and the pathology number, and any other identification should be erased or blackened.

Please ensure that the blocks are carefully packaged as otherwise they could easily get damaged during transport.

Samples have to be sent to the national reference laboratory or directly to:

Pangaea Biotech SA
USP Dexeus Institute
Calle Sabino Arana 5-9
08028-Barcelona, Spain

according to specific instructions in the ***BELIEF procedures manual***.

15.3.2. Submission of serum and plasma samples

Blood collection and serum preparation (see ***BELIEF procedures manual)***:

- Take one SST gel containing tube of 8-10 ml blood
- Keep the tubes for 15-20 minutes at room temperature (until clotting).
- Centrifuge the tubes (1500 g x 10 minutes) and collect the upper phase (supernatant) that corresponds to the serum fraction. Put the supernatant (serum) into appropriately labelled cryovials.

Blood collection and plasma preparation (see ***BELIEF procedures manual)***:

- Take one EDTA containing tube of 8-10 ml blood
- Invert tube several times
- Centrifuge the tube (1500 g x 10 minutes) and collect the upper phase (supernatant) that corresponds to the plasma fraction. Put the supernatant (plasma) into appropriately labelled cryovials.

Serum and plasma samples should be immediately frozen at -80ºC (if a -80ºC is not available, please contact ETOP, see ***BELIEF procedures manual***) and kept at the participating site until shipment. Shipments will be organized centrally.

15.4. Banking of biological material

The ETOP and SCLG have established a central repository for tissue blocks/slides as well as serum and plasma samples from every patient enrolled in this trial. The required pathological material (described in the previous section) is submitted to, catalogued, and maintained in

Pangaea Biotech SA
USP Dexeus Institute
Calle Sabino Arana 5-9
08028-Barcelona, Spain

16. Trial procedures

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

The trial consists of the following stages:

16.1.1. Screening: the screening period must occur within 28 days before registration in the RDE system. Baseline evaluations must be done within 28 days prior to registration. Please consult the ***BELIEF procedures manual*** for a flow chart.

16.1.2. Treatment phase:

Drug therapy is to begin within 7 days of enrolment.

Bevacizumab: 15 mg/kg i.v. on day 1 of each 3-week cycle (+/- 3 days), and erlotinib: 150 mg p.o., daily until progression or unacceptable toxicity.

Upon disease progression or completion of trial treatment, further therapy will be at the discretion of the treating physician.

16.1.3. End of treatment: an end of treatment visit will occur 30 - 40 days following the last dose of study drug.

16.1.4. Follow-up period: every 3 months following end of treatment visit until death, patients will be followed up to document outcome and further lines of treatment. Between end of treatment and progression, the visit schedule needs to follow the one corresponding to the treatment phase, see section 16.7.

16.2. Baseline evaluations (within 28 days prior to registration)

16.2.1. Medical history including symptoms, smoking history, medications, comorbidities and allergies

16.2.2. Physical examination including blood pressure [mmHg], ECOG performance status (see definition in ***BELIEF procedures manual)***, and body weight [kg]

16.2.3. Baseline symptoms

16.2.4. Haematology: haemoglobin, leukocytes, platelets

16.2.5. Renal function: serum creatinine and creatinine clearance calculated according to Cockroft-Gault, urine dipstick for proteinuria

16.2.6. Hepatic function: ALT, AST, AP, Bilirubin

16.2.7. Coagulation: INR

16.2.8. Pregnancy test for women with childbearing potential

16.2.9. CT scan of thorax and upper abdomen with i.v. contrast (alone or in combination with PET) to determine measurable disease according to RECIST v1.1 (at least one lesion outside of irradiated areas that can be measured in at least one dimension as ≥ 10 mm, or ≥ 15 mm in case of lymph nodes). In the presence of clinically suspected metastases outside the thorax (e.g. brain, bone or lower abdomen), additional CT of the affected body part is recommended.

16.2.10. CT scan of brain is not mandatory and only recommended in case of clinically suspected brain metastasis

16.3. Before enrolment

16.3.1. For central confirmation of EGFR exon 19 deletion (del19) or exon 21 mutation (L858R), send to central laboratory:

- 1 block of FFPE tissue from biopsy, surgery or cytology
- Pathology report
- Local EGFR mutation report (if applicable)

16.4. Before start of treatment

16.4.1. Take a blood sample for routine evaluations plus serum and plasma samples for translational research

16.5. Routine evaluations before and during trial treatment

On day 1 of every 3-week treatment cycle:

16.5.1. Recording of symptoms / adverse events

16.5.2. Physical examination including blood pressure, performance status, and body weight

16.5.3. Haematology: haemoglobin, neutrophils, platelets

16.5.4. Serum creatinine

16.5.5. Hepatic function: ALT, AST, AP, Bilirubin

16.5.6. Urine dipstick

16.6. Trial-specific evaluations during treatment

16.6.1. Tumor assessments will occur more frequently during the first cycles, and be phased out especially for patients who stay on treatment for a prolonged period. They should be performed within 72h before the start of the subsequent cycle. Prior to the start of cycles 3, 5, 7, 10, 13, 16, 20, 24, 28 and every 4 cycles until progression (weeks 6, 12, 18, 27, 36, 45, 57, 69, 81; and then every 12 weeks): CT thorax and upper abdomen

16.6.2. Blood serum and plasma samples for translational research have to be taken after 6 weeks (time of first tumor evaluation).

16.7. Evaluations in the follow-up phase before progression

Patients who discontinue treatment before progression should have the following assessments at the same timepoints as patients still on treatment (weeks 6, 12, 18, 27, 36, 45, 57, 69, 81; and every 12 weeks until progression):

16.7.1. Physical examination

16.7.2. CT thorax and upper abdomen (plus further imaging if applicable)

16.7.3. Documentation of further treatments

16.8. Evaluations at progression

Each patient will receive trial treatment until documented progression. At progression, do the following:

16.8.1. CT thorax and upper abdomen, document progression on the respective CRF

16.8.2. Blood serum and plasma samples for translational research

16.8.3. Tumour re-biopsy should be considered for testing of further predictive markers and translational research at the central reference laboratory (Pangaea Biotech)

16.9. End of treatment visit

At the end of the trial treatment and **irrespective of the reason for stopping treatment**, a post treatment visit at the center is to be scheduled after 30 (to 40) days following last treatment day. The following procedures should be performed:

16.9.1. Recording of symptoms/ adverse events

16.9.2. Physical examination including blood pressure

16.9.3. Haematology: haemoglobin, neutrophils, platelets

16.9.4. Hepatic function: ALT, AST, AP, Bilirubin

16.9.5. Serum creatinine

16.9.6. Urine dipstick

16.9.7. CT thorax and upper abdomen, if not done within the last 30 days

16.10. Evaluations after progression

Patients with progression will end trial treatment and should have documented

- survival and
- further lines of treatment

every 12 weeks up to 3 years after the inclusion of the last patient.

17. Case report forms and documentation

17.1. Case report forms schedule

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

Tab in the RDE	**To be completed**
Identification	At screening, prior to enrolment
Eligibility	At screening, prior to enrolment
Baseline	At enrolment
Cycle	At the end of each cycle and at the end of treatment visit (30 - 40 days post trial treatment)
Tumour assessment	At baseline and at start of cycles 3, 5, 7, 10, 13, 16, 20, 24, 28; every 12 weeks until progression in case of treatment discontinuation; at progression Patients who discontinue treatment before progression: at weeks 6, 12, 18, 27, 36, 45, 57, 69, 81; and every 12 weeks until progression At end of treatment visit (if not done within the past 30 days)
End of treatment	30 - 40 days after last treatment day
Adverse event	At the end of each cycle; At the end of treatment visit (30 - 40 days post trial treatment)
Pregnancy	At first documentation of pregnancy; At end of pregnancy At end of treatment visit (if applicable)
SAE initial report	Within 24h of occurrence of SAE to RDE, or via fax to ETOP safety office
SAE follow-up report	Within 14 days after onset; in case the SAE is reported as ongoing after 14 days, the follow-up report has to be submitted again with the final outcome

Tab in the RDE	To be completed
Follow-up	Patients who discontinue treatment before progression: at weeks 6, 12, 18, 27, 36, 45, 57, 69, 81; After progression: At every follow-up visit, every 12 weeks for 3 years

Consult the ***BELIEF Procedures Manual*** for detailed instructions on how to complete, save and submit the electronic CRFs.

18. Statistical considerations

18.1. Primary objective

The goal of the primary analysis is to obtain an estimation of PFS. All eligible and treated patients will be included into this analysis. The overall PFS and the PFS according to T790M status will be determined. The EAST software package is used for sample size calculations (EAST 5, Version 5.4.0.0, Cytel Inc. 2010).

We hypothesize that the trial treatment with bevacizumab and erlotinib will result in

- An increase of the median PFS to 18 months for patients with EGFR T790M mutation
- A median PFS of approximately 18 months or more in patients without EGFR T790M mutation

18.2. Sample size determination

The sample size calculations are based on the percentage of patients with EGFR T790M mutation and corresponding median PFS by EGFR T790M mutation under erlotinib treatment, as presented in the recently published results by Rosell et al (15).

The trial encompasses two phase II substudies run in parallel, and requires a total of 102 patients:

- substudy 1: 35 patients with EGFR T790M mutation
- substudy 2: 67 patients without EGFR T790M mutation.

The first substudy follows Simon's two-stage design and a decision can be reached at the first stage, while the second substudy follows Fleming's single stage design.

Substudy 1: Patients with EGFR T790M mutation

The primary objective is the estimation of PFS in patients with EGFR T790M mutation, treated with bevacizumab and erlotinib. The median PFS is expected to improve to 18 months.

A 12-month PFS of 40%, corresponding to a median of 9 months, will be considered inadequate (since a 12 month median PFS is achieved by erlotinib alone), while the target value will be a 12-month PFS of 63% (corresponding to a median PFS of 18 months, similar to the one observed with erlotinib alone in the subgroup of patients without EGFR T790M mutation). Simon's optimal two-stage design (43), with a significance level of 5% and

power of 80%, will be used to test the null hypothesis that the 12 month PFS≦40% versus the alternative that PFS≧63%.

If in the first stage from a total of 8 patients, 4 or more patients reach 12 months without a progression-defining event, then the substudy will proceed so as to evaluate the 12-month PFS for a total of 35 patients. If 19 or more patients reach 12 months without a PFS event, treatment with the combination of erlotinib and bevacizumab will warrant further study in a Phase III trial in the subgroup of patients with EGFR T790M mutation.

It is anticipated that the decision on the first stage of substudy 1 will not be reached before the study is fully accrued, since 12 months of follow-up will be required for at least 8 patients with EGFR T790M mutation, while the anticipated full study accrual will be completed within 12 months.

In case, the EGFR T790M mutation is identified on only 30% of the patients (instead of the assumed 35%), the decision that can be reached at the end of the study with significance level of 5% and power of 80% will correspond to an alternative of PFS≧66% or a median PFS≧20 months.

Substudy 2: Patients without EGFR T790M mutation

The primary objective is the estimation of PFS in patients with EGFR mutation without T790M mutation, treated with bevacizumab and erlotinib. The median PFS is expected to be approximately 18 months or higher.

A 12-month PFS of 50% will be considered inadequate (since 50% is achieved by erlotinib alone in the subgroup of patients with EGFR T790M mutation), while the target value will be a 12-month PFS of 65% (corresponding to a median PFS of 19 months, similar to the one observed with erlotinib alone in the subgroup of patients without EGFR T790M mutation). A sample size of 67 patients is required by Fleming's single stage design (44), with significance level of 5% and power of 80%, to test the null hypothesis that the 12-month PFS≦50% versus the alternative that PFS≧65%.

Update October 2013:

In patients recruited up to September 2013, the observed proportion with EGFR T790M mutation is higher than originally anticipated at the design stage due to the use of an updated, more sensitive assay. By end of January 2014, the evaluation of PFS will be performed for the patients with EGFR T790M mutation enrolled in the first stage of the substudy 1. If based on that evaluation the substudy 1 continues into the second stage, the trial will accrue 102 patients as planned. Design characteristics of the two substudies will be modified appropriately to accommodate the observed proportion of EGFR T790M mutation.

An additional analysis based on the original, less sensitive assay will also be performed.

18.3. Evaluation of primary and secondary objectives

The total study duration will be approximately 48 months: 12 months recruitment period including a 3 months run-in period, and at least 36 months treatment and follow-up period. The final evaluation of both substudies will be done within 6 months after the last visit of the last patient, approximately 54 months after the inclusion of the first patient.

The primary analysis will be performed separately in the two substudies. The primary efficacy analysis will include all eligible patients with at least two treatment cycles administered (= efficacy cohort). Patients who have been recruited into the trial but are not evaluable for efficacy will be replaced (up to 10% of total sample size).

The two subgroups will also be compared with respect to efficacy and tolerability endpoints.

A secondary analysis will be performed for all registered patients with centrally confirmed EGFR mutation, and will be stratified by EGFR T790M mutation status.

All secondary endpoints will be described for the whole cohort and the two subgroups separately.

Progression free survival (PFS), time to treatment failure (TTF) and overall survival (OS) will be estimated by the Kaplan Meier method and compared between the two subgroups by means of the logrank test.

Clinical efficacy will be further described by objective response rate (ORR), disease control rate (DCR) and duration of response (DR).

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

The correlation of BRCA1 mRNA and AEG-1 mRNA expression and T790M with PFS will be evaluated by univariate and multivariate Cox proportional hazards regression.

The longitudinal development of EGFR mutations (including T790M) in serum and plasma will be evaluated descriptively.

The relation of molecular biomarkers to EGFR TKI and bevacizumab will be explored.

The feasibility of re-biopsies at the time of progression will be reported. Gene-expression arrays for decision-making for second-line treatment will be done in case of available material.

The feasibility of recommending customized second-line chemotherapy based on BRCA1 and AEG-1 mRNA levels will be explored and reported.

18.4. Early stopping rules

Substudy 1 contains an early look at the end of the first stage, when 8 patients have reached 12 months follow-up. If 3 or less patients reach 12 months without a progression-defining event, then the results of the substudy will be reported immediately and the Steering Committee will decide whether the patients still on treatment should stop it. Otherwise the substudy will continue as planned until the final evaluation.

19. Criteria for termination of the trial

19.1. 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 tumor) does not mandate a stop of trial therapy, patients may continue to

receive protocol treatment after appearance of a second primary tumor, 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.

19.2. General criteria for termination of the trial

The trial will be stopped if early analyses of the study data show a significant harm, by decision of ETOP or Trial Steering Committee. The trial can be terminated at any time for safety reasons, insufficient accrual, emerging new data impacting the scientific value of the trial or ethical grounds by Roche or ETOP after consultation of the Trial Steering Commitee.

19.3. 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 ***ETOPdata User Manual***, 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.

20. Ethics approval procedures and Patient Informed Consent

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

20.1. Ethical Review Board/Ethics Committee

The protocol and the use of biological samples from patients must have the approval of a properly constituted committee or committees responsible for approving clinical studies.

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 registration 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.

20.2. Regulatory approval procedures

There will be local, regional and country specific differences in the regulations concerning the use of biological samples for research. Each site will be expected to notify ETOP of the local regulations and seek the relevant approvals.

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 Center activation.

20.3. 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."

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 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 patient should be told that material from her/his tumour, plasma and serum samples will be stored and potentially used for additional studies not described in this protocol.

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 should receive the Institutional Review Board/ Local Ethics Committee approval in advance of its use. Centres should send their locally modified PIS/IC to ETOP for review and approval before submitting to their Ethics Committee.

20.4. Confidentiality/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. 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 labs.

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

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

20.5. Duration of study

Data will be kept in the central database for an unlimited time. The ETOP Foundation Council will decide about the eventual discontinuation of this study and deletion of data.

21. Governance and administrative issues

21.1. 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, SLCG and ETOP officials, representatives from some participating institutions and groups, and a representative from Hoffmann-La Roche.

21.2. Publication

The results of the trial will be published according to the ETOP publication guidelines (appendix 4)

21.3. 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.

21.4. 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 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 study 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, quality of data and storage of plasma and serum samples.

21.5. 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 to the Sponsor 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 the sponsor and approved by the IRB/IEC/REB it cannot be implemented. All protocol deviations will be recorded.

21.6. 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.

22. References

1. La Vecchia C, Bosetti C, Lucchini F, Bertuccio P, Negri E, Boyle P, Levi F. Cancer mortality in Europe, 2000-2004, and an overview of trends since 1975. Ann Oncol. 2010 Jun;21(6):1323-60.

2. Felip E, Gridelli C, Baas P, Rosell R, Stahel R; Panel Members. Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy: 1st ESMO Consensus Conference in Lung Cancer; Lugano 2010. Ann Oncol. 2011 May 20.

3. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-2139

4. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-1500

5. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 2004;101:13306-13311

6. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, Majem M, Lopez-Vivanco G, Isla D, Provencio M, Insa A, Massuti B, Gonzalez-Larriba JL, Paz-Ares L, Bover I, Garcia-Campelo R, Moreno MA, Catot S, Rolfo C, Reguart N, Palmero R, Sánchez JM, Bastus R, Mayo C, Bertran-Alamillo J, Molina MA, Sanchez JJ, Taron M; Spanish Lung Cancer Group. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. 2009 Sep 3;361(10):958-67

7. Rosell R, Gervais R, Vergnenegre A, Massuti B, Felip E, Cardenal F, Garcia Gomez R, Pallares C, Sanchez JM, Porta R, Cobo M, Di Seri M, Garrido Lopez P, Insa A, De Marinis F, Corre R, Carreras M, Carcereny E, Taron M, Paz-Ares LG. Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European Erlotinib Versus Chemotherapy (EURTAC) phase III randomized trial. J Clin Oncol 29: 2011 (suppl; abstr 7503)

8. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009 Sep 3;361(10):947-57.

9. Ku GY, Haaland BA, de Lima Lopes G Jr. Gefitinib vs. chemotherapy as first-line therapy in advanced non-small cell lung cancer: Meta-analysis of phase III trials. Lung Cancer. 2011 May 10. [Epub ahead of print]

10. New 10: Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, Zhang L, You C. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncology 2011;12(8):735-42

11. Keedy VL, Temin S, Somerfield MR, Beasley MB, Johnson DH, McShane LM, Milton DT, Strawn JR, Wakelee HA, Giaccone G. American Society of Clinical Oncology Provisional Clinical Opinion: Epidermal Growth Factor Receptor (EGFR) Mutation Testing for Patients With Advanced Non-Small-Cell Lung Cancer Considering First-Line EGFR Tyrosine Kinase Inhibitor Therapy. J Clin Oncol. 2011 May 20;29(15):2121-7.

12. Kobayashi S, Boggon TJ, Dayaram T, Jänne PA, Kocher O, Meyerson M, Johnson BE, Eck MJ, Tenen DG, Halmos B. EGFR Mutation and Resistance of Non–Small-Cell Lung Cancer to Gefitinib. N Engl J Med. 2005;352(8):786-92

13. Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, King MC. Linkage of early-onset familial breast cancer to chromosome 17q21. Science 1990;250(4988): 1684–9

14. Taron M, Rosell R, Felip E, Mendez P, Souglakos J, Ronco MS, et al. BRCA1 mRNA expression levels as an indicator of chemoresistance in lung cancer. Hum Mol Genet. 2004;13:2443-9

15. Rosell R, Molina MA, Costa C, et al. Pretreatment EGFR T790M Mutation and BRCA1 mRNA Expression in Erlotinib-Treated Advanced Non-Small-Cell Lung Cancer Patients with EGFR Mutations. Clin Cancer Res 2011;17:1160-8

16. Rosell R, Perez-Roca L, Sanchez JJ, Cobo M, Moran T, Chaib I, Provencio M, Domine M, Sala MA, Jimenez U, Diz P, Barneto I, Macias JA, de Las Peñas R, Catot S, Isla D, Sanchez JM, Ibeas R, Lopez-Vivanco G, Oramas J, Mendez P, Reguart N, Blanco R, Taron M.Customized treatment in non-small-cell lung cancer based on EGFR mutations and BRCA1 mRNA expression. PLoS One. 2009;4(5):e5133.

17. Wang B, Matsuoka S, Ballif BA, Zhang D, Smogorzewska A, Gygi SP, Elledge SJ. Abraxas and RAP80 Form a BRCA1 Protein Complex Required for the DNA Damage Response. Science 2007, Vol. 316 no. 5828 pp. 1194-1198

18. Hu G, Wei Y, Kang Y. The multifaceted role of MTDH/AEG-1 in cancer progression. Clin Cancer Res 2009;15:5615-20.

19. Sarkar D, Emdad L, Lee SG, Yoo BK, Su ZZ, Fisher PB. Astrocyte elevated gene-1: far more than just a gene regulated in astrocytes. Cancer Res 2009;69:8529-35.

20. Viteri S, Rosell R, Costa C, Taron M, Sanchez JJ, Benlloch S, Moran T, Massuti B, Camps C, Majem M, Carcereny E, Cardenal F, Gasco A, Mederos N, Magri I, Rolfo CD, Garcia-Campelo MR, Gimenez Capitan A, de Aguirre I, Queralt C. Astrocyte elevated gene 1 (AEG-1) mRNA expression in non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations. J Clin Oncol 29: 2011 (suppl; abstr 10541)

21. Wu LC, Wang ZW, Tsan JT, Spillman MA, Phung A, Xu XL, Yang MC, Hwang LY, Bowcock AM, Baer R. Identification of a RING protein that can interact in vivo with the BRCA1 gene product. Nat Genet. 1996 Dec;14(4):430-40

22. Taron M, Benlloch S, Rosell R, Sanchez JJ, Costa C, Gimenez Capitan A, Mayo C, Bertran-Alamillo J, Molina MA, Massuti B, Camps C, Majem M, Isla D, Santarpia M, Viteri S, Gasco A, Moran T, Carcereny E, Queralt C, de Aguirre I. Identification of AEG-1 and BARD1 as predictors of erlotinib outcome in EGFR-mutant non-small cell lung cancer (NSCLC) by NanoString multiple target profiling. J Clin Oncol 29: 2011 (suppl; abstr 7589)

23. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer N Engl J Med. 2006 Dec 14;355(24):2542-50.

24. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N, Manegold C. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol. 2009 Mar 10;27(8):1227-34. Epub 2009 Feb 2.

25. Crinò L, Dansin E, Garrido P, Griesinger F, Laskin J, Pavlakis N, Stroiakovski D, Thatcher N, Tsai CM, Wu YL, Zhou C. Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study. Lancet Oncol. 2010 Aug;11(8):733-40.

26. Fischbach NA, Spigel D, Brahmer J, Garst J, Robles R, Chung C, Wang L, Sing A, Lynch T, for the ARIES Investigators. Preliminary safety and effectiveness of bevacizumab (BV) based treatment in subpopulations of patients (pts) with non-small cell lung cancer (NSCLC) from the ARIES study: A bevacizumab (BV) treatment observational cohort study (OCS). J Clin Oncol 27:15s, 2009 (suppl; abstr 8040)

27. Herbst RS, O'Neill VJ, Fehrenbacher L, Belani CP, Bonomi PD, Hart L, Melnyk O, Ramies D, Lin M, Sandler A. Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non small-cell lung cancer. J Clin Oncol. 2007 Oct 20;25(30):4743-50. Epub 2007 Oct 1.

28. Dingemans AM, de Langen AJ, van den Boogaart V, Marcus JT, Backes WH, Scholtens HT, van Tinteren H, Hoekstra OS, Pruim J, Brans B, Thunnissen FB, Smit EF, Groen HJ. First-line erlotinib and bevacizumab in patients with locally advanced and/or metastatic non-small-cell lung cancer: a phase II study including molecular imaging. Ann Oncol. 2011 Mar;22(3):559-66. Epub 2010 Aug 11.

29. Zappa F, Droege C, Betticher DC, von Moos R, Brutsche MH, Baty F, Bubendorf L, Ochsenbein A, Oppliger Leibundgut E, Gautschi O, Froesch P, Stahel RA, Rauch D, Schmid P, Mayer M, Crowe S, Brauchli P, Ribi K, Pless M. Bevacizumab (B) and erlotinib (E) as first-line therapy in metastatic nonsquamous non-small cell lung cancer (NSCLC) followed by platinum-based chemotherapy (CT) at disease progression (PD): A multicenter phase II trial, SAKK 19/05. J Clin Oncol 29: 2011 (suppl; abstr 7561)

30. Naumov GN, Nilsson MB, Cascone T, Briggs A, Straume O, Akslen LA, Lifshits E, Byers LA, Xu L, Wu HK, Jänne P, Kobayashi S, Halmos B, Tenen D, Tang XM, Engelman J, Yeap B, Folkman J, Johnson BE, Heymach JV. Combined vascular endothelial growth factor receptor and epidermal growth factor receptor (EGFR) blockade inhibits tumor growth in xenograft models of EGFR inhibitor resistance. Clin Cancer Res 2009;15:3484-94.

31. Ziegler A, Zangemeister-Wittke U, Stahel RA. Circulating DNA: a new diagnostic gold mine? Cancer Treat Rev. 2002 Oct;28(5):255-71.

32. Sozzi G, Conte D, Leon M, Ciricione R, Roz L, Ratcliffe C, Roz E, Cirenei N, Bellomi M, Pelosi G, Pierotti MA, Pastorino U. Quantification of free circulating DNA as a diagnostic marker in lung cancer. J Clin Oncol. 2003 Nov 1;21(21):3902-8.

33. Gautschi O, Bigosch C, Huegli B, Jermann M, Marx A, Chassé E, Ratschiller D, Weder W, Joerger M, Betticher DC, Stahel RA, Ziegler A. Circulating deoxyribonucleic Acid as prognostic marker in non-small-cell lung cancer patients undergoing chemotherapy. J Clin Oncol. 2004 Oct 15;22(20):4157-64.

34. Ramirez JL, Rosell R, Taron M, Sanchez-Ronco M, Alberola V, de Las Peñas R, Sanchez JM, Moran T, Camps C, Massuti B, Sanchez JJ, Salazar F, Catot S; Spanish Lung Cancer Group. 14-3-3sigma methylation in pretreatment serum circulating DNA of cisplatin-plus-gemcitabine-treated advanced non-small-cell lung cancer patients predicts survival: The Spanish Lung Cancer Group. J Clin Oncol. 2005 Dec 20;23(36):9105-12.

35. Gautschi O, Huegli B, Ziegler A, Gugger M, Heighway J, Ratschiller D, Mack PC, Gumerlock PH, Kung HJ, Stahel RA, Gandara DR, Betticher DC. Origin and prognostic value of circulating KRAS mutations in lung cancer patients. Cancer Lett. 2007 Sep 8;254(2):265-73.

36. Salazar F, Molina MA, Sanchez-Ronco M, Moran T, Ramirez JL, Sanchez JM, Stahel R, Garrido P, Cobo M, Isla D, Bertran-Alamillo J, Massuti B, Cardenal F, Manegold C, Lianes P, Trigo JM, Sanchez JJ, Taron M, Rosell R. First-line therapy and methylation status of CHFR in serum influence outcome to chemotherapy versus EGFR tyrosine kinase inhibitors as second-line therapy in stage IV non-small-cell lung cancer patients. Lung Cancer. 2011 Apr;72(1):84-91.

37. Camps C, Jantus-Lewintre E, Cabrera A, Blasco A, Sanmartín E, Gallach S, Caballero C, del Pozo N, Rosell R, Guijarro R, Sirera R. The identification of KRAS mutations at codon 12 in plasma DNA is not a prognostic factor in advanced non-small cell lung cancer patients. Lung Cancer. 2011 Jun;72(3):365-9.

38. Kuang Y, Rogers A, Yeap BY, Wang L, Makrigiorgos M, Vetrand K, Thiede S, Distel RJ, Jänne PA. Noninvasive detection of EGFR T790M in gefitinib or erlotinib resistant non-small cell lung cancer. Clin Cancer Res 2009;15:2630

39. Bindra RS, Gibson SL, Meng A, Westermark U, Jasin M, Pierce AJ, Bristow RG, Classon MK, Glazer PM. Hypoxia-induced down-regulation of BRCA1 expression by E2Fs. Cancer Res 2005;65:11597-604.

40. Chan N, Koritzinsky M, Zhao H, Bindra R, Glazer PM, Powell S, Belmaaza A, Wouters B, Bristow RG. Chronic hypoxia decreases synthesis of homologous recombination proteins to offset chaemoresistance and radioresistance. Cancer Res 2008;68:605-14.

41. Bindra RS, Glazer PM. Repression of RAD51 gene expression by E2F4/p130 complexes in hypoxia. Oncogene 2007;26:2048-57.

42. Hegan DC, Lu Y, Stachelek GC, Crosby ME, Bindra RS, Glazer PM. Inhibition of poly(ADP-ribose) polymerase down-regulates BRCA1 and RAD51 in a pathway mediated by E2F4 and p130. Proc Natl Acad Sci U S A 2010;107:2201-6.

43. Simon, R. Optimal two-stage designs for Phase II clinical trials. Controlled Clinical Trials, 1989;10:1-10.

44. Fleming, TR. One-sample multiple testing procedure for Phase II clinical trials. Biometrics, 1982; 38:143-151.