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CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER MO22097

An Open-Label, Randomized, Phase IIIb Trial Evaluating The Efficacy And Safety Of Standard of Care ± Continuous Bevacizumab Treatment Beyond Progression Of Disease In Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) After First-Line Treatment With Bevacizumab Plus A Platinum Doublet-Containing Chemotherapy (MO22097)

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PROTOCOL APPROVAL

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Protocol approved by:

Ahmed Kotb, M.D. Roche International Medical Director	18/Aug/2014 Date:
Larry Leon, PhD Statistician	18 Aug. 2014 Date:

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

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GLOSSARY OF ABBREVIATIONS

18FDG	[18]-fluorodeoxyglucose
AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase
b.i.d.	Twice daily
BP	Blood pressure
BSC	Best Supportive Care
Cbar	Average Concentration
CD31	Blood vessel marker to characterize the intratumoral vasculature i.e. micro vessel density
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum plasma concentration
cMET	cMET is the receptor for hepatocyte growth factor. They play an important role in tumor proliferation, invasion and metastasis.
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine clearance
CT	Computed tomography
CVA	Cerebrovascular accident
CVAD	Central venous access device
CXR	Chest X-ray
DCIS	Ductal carcinoma in situ
DLT	Dose-limiting toxicity
DR	Duration of response
EC_{50}	Plasma concentration associated with half-maximal effect
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer

GLOSSARY OF ABBREVIATIONS

ESF	Eligibility screening form
EU	European Union
EUDRACT	European Union Drug Regulating Authorities Clinical Trials
FBC	Full blood count
FDA	Food and Drug Administration
Flt-1	Fms-like Tyrosine Kinase
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
HR	Hazard ratio
IB	Investigator's brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IND	Investigational new drug
INR	International normalized ratio
IRB/IEC	Institutional Review Board / Independent Ethics Committee
ITT	Intent-to-treat
i.v.	Intravenous
LPFV	Last patient's first visit
mBC	Metastatic breast cancer
mCRC	Metastatic colorectal cancer
MedDRA	**Medical Dictionary for Regulatory Activities**
mRCC	Metastatic renal cell carcinoma
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRI	Magnetic resonance image
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Toxicity Criteria for Adverse Events
NRP	Neuropilin
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival

GLOSSARY OF ABBREVIATIONS

PD	Progression of disease / progressive disease
PD1/2	First/second progression of disease
PET	Positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetic
PlGF	Placental growth factor
p.o.	Oral administration
PP	Per Protocol
PR	Partial response / Pulse rate
PS	Performance status
Q3W	Every 3 weeks
QoL	Quality of life
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	Reversible posterior leucoencephalopathy syndrome
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analyses Plan
SCr	Serum creatinine
SD	Stable disease
SmPC	Summary of product characteristics
SMT	Study management team
SOC	Standard of care
SPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
SWFI	Sterile water for injection
TTP	Time to disease progression
ULN	Upper limit of normal
USP	United States Pharmacopeia
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood count
WOCP	Women of child-bearing potential

SYNOPSIS OF PROTOCOL

TITLE	An open-label, randomized, Phase IIIb trial evaluating the efficacy and safety of standard of care ± continuous bevacizumab treatment beyond progression of disease (PD) in patients with advanced non-squamous non-small cell lung cancer (NSCLC) after first (1st)-line treatment with bevacizumab plus a platinum doublet-containing chemotherapy
SPONSOR	F. Hoffmann-La Roche Ltd. CLINICAL PHASE IIIb
INDICATION	Locally recurrent or metastatic non-squamous NSCLC which has progressed beyond 1st-line treatment with bevacizumab plus a platinum doublet-containing chemotherapy regimen and bevacizumab (monotherapy) maintenance treatment
OBJECTIVES	Primary: • To assess the efficacy of continuous bevacizumab treatment beyond PD1 as measured by overall survival (OS). Secondary: • To assess the efficacy as measured by rate of 6-, 12-, and 18-month OS as measured from randomization at 1st progression of disease (PD1). • To assess the efficacy as measured by progression free survival (PFS) and time to progression (TTP) from randomization at PD1, to second (2nd) PD (PD2) (PFS2, TTP2), and to third (3rd) PD (PD3) • To assess the efficacy as measured by response rates (RRs), disease control rates, and duration of response at PD2 and PD3. • To assess the efficacy in the subgroup of adenocarcinoma patients. • To assess the safety of bevacizumab treatment across multiple lines of treatment. Exploratory: • To assess quality of life (QoL) through multiple lines of treatment. • To compare the efficacy between Asian and non-Asian patients. Exploratory analyses related to biomarkers: • Specimens taken for biomarker research will be

	used to: o explore the correlation of biomarkers with response rate, PFS and OS. o investigate early, intermediate and late escape mechanisms related to bevacizumab in combination with standard of care (SOC) treatment regimen o explore the association between biomarkers and disease response and adverse events o develop biomarker assays and to establish the performance characteristics of these assays Additional analyses will be specified in the Statistical Analysis Plan.
TRIAL DESIGN	Multicenter, open-label, randomized, two-arm, phase IIIb trial. Patients will be enrolled at documentation of PD1 after 4-6 cycles of 1st-line treatment with bevacizumab plus a platinum doublet-containing chemotherapy regimen and a minimum of two cycles of bevacizumab (monotherapy) maintenance treatment prior to PD1. Patients will be randomized in a 1:1 ratio to receive either bevacizumab plus agents indicated for use in 2nd and subsequent lines of treatment (hereafter referred to as SOC treatment), or SOC treatment alone. No crossover is permitted.
NUMBER OF PATIENTS	Approximately 500 patients
NUMBER OF CENTERS	Approximately 160 centers
TARGET POPULATION	Patients with locally recurrent or metastatic non-squamous NSCLC.
LENGTH OF TRIAL	Recruitment period: Approximately 45 months. Observation period: until 416 deaths are reported, or 60 months from study start, whichever occurs first. All patients will be followed until death, loss to follow-up, or trial termination.
END OF TRIAL	Until completion of observation period, or until the last patient dies, whichever occurs first.
INVESTIGATIONAL MEDICAL PRODUCT(S) DOSE / ROUTE / REGIMEN	Each cycle will have a duration of 21 days. The approved (per label) dose (7.5 or 15 mg/kg i.v.) and Q3W schedule of bevacizumab used during 1st-line and maintenance treatment should be the same dose and schedule administered to each patient during the study. The same bevacizumab dose and Q3W schedule must be continued throughout all lines of treatment. Patients with documented PD after 4-6 cycles of 1st-line treatment with bevacizumab plus a platinum

	doublet-containing chemotherapy regimen and a minimum of two cycles of bevacizumab (monotherapy) maintenance treatment prior to PD will be randomized (1:1) as follows: • Arm A: Bevacizumab 7.5 or 15 mg/kg i.v. on Day 1 every 21 days (± 3 days) plus investigator's choice of SOC agent indicated for use in 2nd and subsequent lines of treatment. Beyond PD3, bevacizumab may be continued through subsequent lines of treatment at the investigator's discretion in the absence of unacceptable toxicity or consent withdrawal. • Arm B: investigator's choice of SOC agent indicated for 2nd-line use on Day 1 every 21 days (± 3 days). Subsequent lines of treatment and corresponding administration schedules will be selected based on local practice. Patients randomized to Arm B may not receive bevacizumab.
NON-INVESTIGATIONAL MEDICAL PRODUCT(S)	Labelled SOC agents for 2nd-line treatment for NSCLC will be limited to erlotinib, docetaxel or pemetrexed. Only one agent may be used in any given Cycle, but substitution is permitted for toxicity. All 2nd-line agents need to be given on Day 1 every 21 days (± 3 days). Labelled SOC agents for 3rd-line and beyond treatment for NSCLC will be chosen by the investigator, and will be administered according to local practice.
COMPARATOR "DRUG" (or STANDARD OF CARE) DOSE/ ROUTE/ REGIMEN	This trial is comparing SOC plus bevacizumab vs. SOC for patients who have progressed after completion of 1st-line treatment with bevacizumab plus a platinum doublet-containing chemotherapy regimen and a minimum of two cycles of bevacizumab (monotherapy) maintenance treatment.
INCLUSION CRITERIA	1. Signed informed consent prior to initiation of any trial-specific procedure or treatment. 2. Age ≥ 18 years. 3. Ability to comply with the protocol. 4. Histologically or cytologically (sample to be obtained by biopsy or bronchoscopy, no rebiopsy is needed at PD1) confirmed non-squamous NSCLC with documented PD (locally recurrent or metastatic) per investigator assessment following 1st-line treatment with 4-6 cycles of bevacizumab plus a platinum doublet-containing chemotherapy regimen and a minimum of 2 cycles of bevacizumab (monotherapy) maintenance treatment prior to PD1. 5. No treatment interruption of bevacizumab treatment greater than 42 days between the start

of 1st-line treatment to start of Cycle 1 of 2nd-line treatment.

6. Randomization within 4 weeks of PD1.
7. At least 1 unidimensionally measurable lesion meeting RECIST (v.1.1) criteria.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-2.
9. Life expectancy ≥ 16 weeks by investigator assessment.
10. Adequate hematological function:
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    - Platelet count ≥ 100 x 10^9/L
    - Hemoglobin ≥ 9 g/dL (may be transfused to maintain or exceed this level).
11. Adequate liver function:
    - Total bilirubin < 1.5 x upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 x ULN in patients without liver metastases; < 5 x ULN in patients with known liver metastases.
    - Alkaline phosphatase (ALP) < 2.5 x ULN (< 5 x ULN for patients with known liver involvement and < 7 x ULN for patients with known bone involvement).
12. Adequate renal function:
    - Serum creatinine ≤ 1.25 x ULN or calculated creatinine clearance ≥ 50 mL/min
    - Urine dipstick for proteinuria < 2+. Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate < 1 g of protein in 24 hours.
13. International normalized ratio (INR) ≤ 1.5 and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN within 7 days prior to randomization, unless there is prophylactic use of anti-coagulation. If local standards differ, equivalent coagulation tests may be used.
14. Patients with asymptomatic treated brain metastases are eligible for trial participation. Patients must complete treatment for brain metastases (radiotherapy or stereotactic radiosurgery), including steroids, at least 14 days prior to randomization. Treatment with anticonvulsants at the time of randomization (i.e. ≥ 28 days) is allowed as long as the anti-convulsant is at a stable dose).
15. Female patients must not be pregnant or breast-

	feeding. Female patients of childbearing potential (defined as < 2 years after last menstruation or not surgically sterile) must use a highly effective contraceptive method (allowed methods of birth control, i.e. with a failure rate of less than 1% per year, are implants, injectables, combined oral contraceptives, intra-uterine device [IUD; only hormonspirals], sexual abstinence or vasectomized partner) during the trial and for a period of at least 6 months following the last administration of trial drug(s). Female patients with an intact uterus (unless amenorrhoeic for the last 24 months) must have a negative serum pregnancy test within 7 days prior to randomization into the trial. 16. Fertile male patients must agree to use a highly effective contraceptive method (allowed methods of birth control, i.e. with a failure rate of less than 1% per year, include a female partner using implants, injectables, combined oral contraceptives, IUDs [only hormonspirals], sexual abstinence or prior vasectomy) during the trial and for a period of at least 6 months following the last administration of trial drug(s).
EXCLUSION CRITERIA	1. Mixed, non-small cell and small cell tumors or mixed adenosquamous carcinomas with a predominant squamous component. 2. EGFR-mutation-positive disease according to local laboratory testing. EGFR testing is not mandatory. In centers where this is not routinely done, patients with unknown EGFR mutation status are allowed to participate in this trial. 3. History of pulmonary hemorrhage/hemoptysis ≥ grade 2 (defined as bright red blood of at least 2.5 mL) within 3 months prior to randomization. 4. Surgery (including open biopsy), significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during trial treatment. 5. Minor surgery, including insertion of an indwelling catheter, within 24 hours prior to the first bevacizumab infusion. 6. Evidence of tumor invading a major blood vessel (e.g., pulmonary artery or superior vena cava) on imaging. 7. Radiotherapy to any site for any reason within 28 days prior to randomization. Palliative radiotherapy to bone lesions or the brain ≥ 14 days prior to randomization is allowed. 8. Current or recent (within 10 days prior to first dose of bevacizumab) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day), or

current or recent (within 10 days prior to first dose of bevacizumab) use of full-dose (i.e. therapeutic dose) oral or parenteral anticoagulants or thrombolytic agent for therapeutic purposes. Prophylactic use of anticoagulants is allowed.

9. History or evidence of inherited bleeding diathesis or coagulopathy with a risk of bleeding.
10. Active gastrointestinal bleeding
11. Inadequately controlled hypertension (blood pressure: systolic > 150 mmHg and/or diastolic > 100 mmHg) within 28 days prior to randomization or history of hypertensive crisis or hypertensive encephalopathy
12. Clinically significant (i.e. active) cardiovascular disease (e.g. cerebrovascular accident [CVA] or myocardial infarction within 6 months prior to randomization, unstable angina, congestive heart failure [CHF] New York Heart Association [NYHA] Class ≥ II, or serious cardiac arrhythmia – see Appendix 8), that is uncontrolled by medication or may interfere with administration of trial treatment.
13. Non-healing wound, active skin ulcer or untreated bone fracture.
14. History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to randomization.
15. Treatment with any other investigational agent within 28 days prior to randomization. Patients in the follow-up phase of 1st-line trials who fulfill all eligibility criteria may be enrolled in this trial if the 1st-line protocol allows bevacizumab-based treatment in the follow-up phase.
16. Known hypersensitivity to bevacizumab or any of its excipients, or any of the SOC agents foreseen.
17. Malignancy other than NSCLC within 5 years prior to randomization, except for adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated with curative intent, and ductal carcinoma in situ (DCIS) treated surgically with curative intent.
18. Evidence of any other disease, neurologic or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational or SOC drug used in this study or puts the patient at higher risk for treatment-related complications.

ASSESSMENTS OF:	
– EFFICACY	Clinical assessments will include prior medical history, prior cancer treatment and ECOG PS. Tumor assessment and evaluation: • Evaluation will be performed using RECIST (v.1.1) criteria (see Appendix 1). Any response that is detected will be confirmed by a follow-up scan at least 4 weeks later. • CT scans of chest and upper abdomen using i.v. contrast will be performed at baseline. Other modalities should be used as appropriate to ensure that all known and suspected sites of disease are adequately imaged and followed for signs of PD per RECIST v1.1. Tumor assessments must be performed using the same imaging technique for a patient, throughout the trial. • Isotope bone scan at baseline for patients known to have bone metastasis, or displaying clinical or biological signs (e.g., serum alkaline phosphatase [ALP] > 1.5 ULN) of bone metastasis. This procedure is not mandatory if an [18]-fluorodeoxyglucose (18FDG) positron emission tomography (PET) scan has already been performed. • Tumor assessments may also include a respective CT / MRI scan of the brain in patients with symptoms/signs suggestive of central nervous system (CNS) involvement or other unexplained neurological symptoms. To assess response rates and durations for 2nd-line efficacy, evaluations will use the tumor assessment confirming PD1 as baseline (i.e. the latest assessment prior to Cycle 1 of 2nd-line treatment). To assess response rates and durations for 3rd-line efficacy, evaluations will take the tumor assessment confirming PD2 as baseline (i.e. the latest assessment prior to cycle 1 of 3rd-line treatment).
– SAFETY	All assessments will be performed as described in the Schedule of Assessments (Table 1). Additional assessments may be performed as clinically indicated. Data regarding significant medical history and medical conditions and all ongoing adverse events (AEs) and resolved AEs grade ≥ 3 documented during 1st-line and maintenance treatment will be collected. All AEs will be assessed using the National Cancer Institute Common Terminology Criteria for AEs (NCI CTC-AE) criteria (v. 4.0). All grades of AEs, serious

	adverse events (SAEs), and AEs of special interest will be documented at each visit throughout the entire trial. The incidence of SAEs and non-SAEs related to bevacizumab and/or SOC agents will be determined. Additional information about AEs of special interest (serious and non-serious) such as: • Hypertension • Reversible Posterior Leucoencephalopathy Syndrome (RPLS) • Proteinuria • Hemorrhage, with a focus on hemoptysis and CNS bleeding • Arterial and venous thromboembolic events • Wound healing complications • Gastro-intestinal perforation • Fistulae • CHF will be captured. They will be followed up for 6 months after the last bevacizumab administration. CT / MRI scan of the brain is not mandatory but should be performed if there is a clinical suspicion of CNS metastasis. Left ventricular ejection fraction (LVEF) will only be assessed in the event of symptomatic CHF and should be repeated every 3 weeks until resolution or stabilization of the event. An independent Data Monitoring Committee (IDMC) will ensure the safety and tolerability of the trial regimen. A first safety assessment is planned after 150 randomized patients (approximately 75 per arm) have been on trial for at least 2 months. Thereafter safety assessments will be performed every 6 months. The IDMC will adapt a safety review schedule if appropriate.
– PHARMACOKINETICS / PHARMACODYNAMICS	Not applicable (NA)
– QUALITY OF LIFE (QoL)	QoL using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30/QLQ-LC13 questionnaire will be assessed at the time points listed in the Schedule of Assessments (Table 1).
– EXPLORATORY BIOMARKERS (non-DNA)	This as an optional part of the trial for which patients will provide additional consent. Roche Clinical Repository (RCR) blood and plasma samples will be collected from consenting patients at baseline (after documented PD1 and before randomization) and after randomization every 4

	cycles (12 weeks) until end of treatment to: • investigate early, intermediate and late escape mechanisms related to bevacizumab and SOC regimen • investigate the association of biomarkers with response and adverse reactions • develop biomarker assays and to establish the performance characteristics of these assays. Sampling will stop in patients continuing treatment beyond 4th-line. New markers are continually being recognized as potentially correlating with efficacy disease activity, safety or escape from treatment. The definitive list of analyses remains to be determined, but may include determination of markers of angiogenesis (e.g. VEGF, VEGFR-1, VEGFR-2, neuropilins, angiopoetins, PlGF). All exploratory samples will be stored in the RCR, which is a centrally administered facility used for the long term storage of human biological specimens. All RCR specimen(s) will be destroyed no later than 15 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period.
– EXPLORATORY BIOMARKERS (DNA)	This as an optional part of the trial for which patients will provide additional consent. One specimen for inherited biomarker discovery will be collected from all patients participating in this clinical trial for pharmacogenetic and genetic research before treatment start. RCR DNA sampling will depend on the approval of local ethic committees. Polymorphisms of VEGF, VEGF receptors and related genes have been evaluated in various indications, including breast, gastric and renal cancer either as prognostic or risk markers with variable success. Recent analysis of polymorphisms in the VEGF gene has revealed an association with various genotypes and better OS. All exploratory samples will be stored in the RCR, which is a centrally administered facility used for the long term storage of human biological specimens. All RCR specimen(s) will be destroyed no later than 15 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period.
– EXPLORATORY BIOMARKERS (TISSUE)	This as an optional part of the trial for which patients will provide additional consent. Tissue sampling will depend on the central/local approval following the country specific regulations. The following assessments may be performed but

	are not limited to: • Expression of neuropilin (NRP) 1 • Expression of VEGF (Vascular Endothelial Growth Factor) • Expression of VEGF-R1 (VEGF- Receptor) • Expression of VEGF-R2 • Expression of CD31 • Expression of cMet Additional methodologies may be applied for corroboration, including RT-PCR (Reverse transcriptase polymerase chain reaction), in situ hybridization, and gene expression profiling. The collected tumor tissue may be used to develop diagnostic assays and might allow the generation of statistically meaningful biomarker data. All exploratory samples will be stored in the RCR, which is a centrally administered facility used for the long term storage of human biological specimens. All RCR specimen(s) will be destroyed no later than 15 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period.
– CLINICAL GENOTYPING (CG) SAMPLES	NA
– MANDATORY BIOMARKER SAMPLES	NA
RANDOMIZATION PROCEDURES	Patients with documented PD1 will be randomized (1:1) via an IW/VRS system, through a central stratified block randomization process using the following stratification factors: • Type of planned 2nd-line SOC treatment (erlotinib vs. docetaxel vs. pemetrexed) • Number of cycles of bevacizumab maintenance treatment (≤ 6 vs. > 6) • Smoking status (never vs. former vs. current)
STATISTICAL ANALYSES:	Sample size considerations: The sample size calculation for this trial is based on a 45-month recruitment period and minimum follow-up of 12 months. Assuming a median OS beyond progression (PD1) of 10 months (1 year OS rate 43.5%) in the control group, and 12.8 months (1 year OS rate 52.3%) in the treatment arm (corresponding to a hazard ratio of 0.78) then approximately 416 events are required to achieve 80% power for the log-rank test at a one-sided significance level of 5%. To allow for a 2% drop-out rate, approximately 500 patients are required (250 per treatment arm). Under the study

assumptions the time to observe 416 events is estimated to be 57 months. The final efficacy analysis will be conducted when either 416 events are observed or after 60 months study duration, whichever occurs first.

Efficacy:

The primary and secondary efficacy endpoint analyses will be performed on the intent-to-treat (ITT) population, defined as all consenting patients randomized to trial treatment.

The primary efficacy analysis for this trial will compare duration of OS beyond progression for bevacizumab plus SOC treatment or SOC treatment alone.

The duration of PFS (PFS2, PFS3) for patients who have not died (or are not known to have died, or are lost to follow-up) at the time of analysis will be censored as of the date the patient was last known to be progression-free. Differences in PFS between treatment arms will be tested with a stratified log-rank test (stratified on the stratification factors used at randomization). Kaplan-Meier curves will be displayed, with median PFS estimates and confidence limits provided.

OS will be summarized by Kaplan-Meier curves. Median survival estimates as well as associated 90% confidence intervals (CIs) will be reported for each treatment arm. The OS estimates and corresponding 90% CIs at 6-, 12- and 18 month will be also presented. The difference in OS between the treatment arms will be tested with a stratified log-rank test.

Response rates and disease control rates will be summarized by treatment arm and the estimated difference in response rates and the associated 90% CIs will be provided. The Cochran-Mantel Haenszel test, stratified by the same factors used at randomization will be used to compare the overall response rate between the treatment arms. An unadjusted Chi-squared test result will also be provided.

Differences in duration of response will be tested for descriptive purposes with a stratified log-rank test. Kaplan-Meier curves will be displayed, with median duration estimates and confidence limits provided.

The efficacy analysis described above will be also shown for the subgroup of:

- adenocarcinoma patients
- Asian and non-Asian patients.

More details will be specified in the Statistical

Analysis Plan.

Safety:

All safety parameters will be presented based on the safety population, defined as all patients who received at least one dose of trial drug after randomization.

AEs will be presented in frequency tables. Laboratory data will be presented as summary statistics for each sampling time point using both shift and frequency tables. All AEs and abnormal laboratory variables will be assessed using the NCI CTC-AE v.4.0.

Descriptive statistics will be used to summarize ECOG PS.

Vital signs will be presented in listings as well as in summaries by time windows.

Information on trial drug will be summarized by duration, starting dose and cumulative dose using descriptive statistics.

Exploratory analyses will be done on all patients who received at least one dose of trial drug after enrollment.

Quality of Life (QoL):

QoL will be assessed using the core module, EORTC QLQ-C30, and lung cancer specific module, QLQ-LC13.

The QoL scales will be summarized by descriptive summary tables at baseline (randomization at PD1) and over time. Mixed model repeated measures will be used to compare between arms in 2nd-line and between lines of treatment. Missing data will be handled according to the EORTC User's Manual.

The proportion of patients with improvement, degradation, or no change in their health related QoL will be summarized by descriptive summary tables at baseline and over time. The Cochran-Mantel Haenszel test stratified by the same factors used to stratify the randomization will be used to compare the response rates between the treatment arms at the end of treatment. An unadjusted Chi-squared test result will also be provided. To demonstrate time-to-deterioration in health-related QoL, Kaplan-Meier will be used to estimate median time to deterioration and stratified log-rank test will be used to compare the distribution of time-to-deterioration between treatment arms.

Biomarker Analysis:

	The analysis of the biomarkers will be performed in order to evaluate the prognostic value of each analyzed marker. Descriptive analysis will be conducted first. The association between each biomarker and prognosis will be analyzed by Cox proportion hazards model and logistic regression for time-to-event endpoints and tumor response endpoints, respectively. The interaction between treatment and each of the biomarkers on prognosis will also be assessed. Exploratory descriptive and graphical analyses of the time course of plasma biomarkers and tumor size assessments will be produced. Additional analyses will be specified in the Statistical Analysis Plan.

PROCEDURES (summary):

Informed consent

Written, informed consent must be obtained before patients undergo any trial-related procedures.

If site and patient agree to participate in the optional biomarker portion of the protocol, a separate, written biomarker-specific informed consent must be obtained from the patient.

Screening / baseline period:

Only after provision of written, informed consent, potential participants will undergo the following screening procedures no more than 28 days (unless otherwise noted) prior to their first trial treatment, unless they have already been conducted within 28 days prior to their first trial treatment as part of the patient's routine clinical care:

- Demographics (including ethnicity), complete medical history, concurrent illnesses.
- Lung cancer history, including smoking history, prior surgery, radiotherapy, chemotherapy and other anti-tumor treatment, AEs experienced during 1st-line treatment with 4-6 cycles of bevacizumab plus a platinum doublet-containing chemotherapy regimen, followed by a minimum of 2 cycles of bevacizumab (monotherapy) maintenance prior to PD1 (ongoing AEs all grades; resolved AEs grade ≥ 3, to be reported in medical history), results of histological/cytological analyses, tumor location and staging, and genetic information (e.g. EGFR mutation status) if available.
- Standard 12-lead electrocardiogram (ECG).
- Complete physical examination and measurement of vital signs (including height, weight and blood pressure).
- ECOG PS assessment.
- Clinical laboratory testing should include:
  - hematology (i.e. hemoglobin, hematocrit, red blood cell count, white blood cell count including differential, platelet count)
  - coagulation tests (INR and aPTT or equivalent)

- serum chemistry (including total protein [or albumin only], AST/SGOT, ALT/SGPT, ALP, total bilirubin, creatinine; Creatinine clearance will be calculated)
- urinalysis by dipstick. In case proteinuria ≥ 2+ is detected by the dipstick method, a 24-hour urine collection is needed to confirm renal function is within acceptable limits (≤ 1 g per day).

- Pregnancy test: Women of childbearing potential will have a serum pregnancy test no more than 7 days prior to the first trial treatment or no more than 14 days (with a confirmatory urine pregnancy test within 7 days prior to Day 1, Cycle 1). This is not required for women who have undergone, and have documentation of, a hysterectomy.
- Tumor assessment and evaluation: Evaluation will be performed using RECIST (v.1.1) criteria (see Appendix 1) within 28 days prior to the first dose of trial drug treatment, with the aim being to assess tumor burden as close to the first dose as possible.
  - CT scans of chest and upper abdomen using i.v. contrast will be performed at baseline. Tumor assessments must be performed using the same imaging technique throughout the trial.
  - PET scans and ultrasounds may not be used for tumor measurements
  - Isotope bone scan at baseline for patients known to have bone metastasis, or displaying clinical or biological signs (e.g., serum ALP > 1.5 ULN) of bone metastasis. This procedure is not mandatory if an ^{18}FDG PET scan has already been performed.
  - CT / MRI scan of the brain is not mandatory but should be performed if there is a clinical suspicion of CNS metastasis.
- Adverse events: After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in). All other AEs should be documented with the medical history.
- QoL (EORTC QLQ-C30/QLQ-LC13).
- RCR sampling (optional):
  - non-genetic plasma samples (2 x 6 mL); and
  - a genetic whole blood sample (6 mL).
  - 20 slides of formalin fixed tumor tissue embedded in paraffin blocks

Randomization

- After confirming eligibility, and after choice of 2nd-line SOC therapy, patients will be randomized (details see Section 5.2) in a 1:1 fashion to either
  - Arm A: Bevacizumab 7.5 mg/kg i.v. or 15 mg/kg i.v. on Day 1 every 21 days (± 3 days) together with SOC treatment

  or
  - Arm B: SOC treatment alone, every 21 days (± 3 days) for 2nd-line treatment. SOC cycle length beyond 2nd-line treatment will be according to local practice.

Treatment phase (2nd and later lines):

Note: for the purposes of scheduling assessments and visits for 3rd-line treatment and beyond (as the SOC treatment may not be based on a 3-week cycle), "cycles" are based on bevacizumab scheduling for Arm A. In Arm B, patient's visits should occur Q3W if possible, regardless of the SOC treatment schedule.

Prior to each trial drug administration (or every 3 weeks if SOC agent is not based on a Q3W schedule), patients will undergo the following assessments according to the Assessment Schedule:

- Standard 12-lead ECG only if clinically indicated.
- LVEF will only be assessed in the event of symptomatic cardiac failure and should be repeated every 3 weeks until resolution or stabilization of the event. Same assessment method should be used throughout the trial.
- Complete physical examination and measurement of vital signs (weight and blood pressure) no more than 3 days prior to Day 1 of each Cycle.
- ECOG PS assessment at the commencement of each cycle and at progression of disease.
- Clinical laboratory testing, no more than 7 days prior to Day 1 of Cycle 1 and within 3 days of Day 1 of each subsequent Cycle, should include:
    - hematology (e.g. hemoglobin, hematocrit, red blood cell count, full white blood cell count including differential, platelet count)
    - coagulation tests (INR and aPTT or equivalent) when clinically indicated (Patients receiving full doses of coumarin derivatives at baseline should have two consecutive INR measurements 1–4 days apart. Coagulation tests for the patient on (prophylactic or full dose) anticoagulation treatment should be done at least before start of every SOC cycle.)
    - serum chemistry (including total protein [or albumin only], AST/SGOT, ALT/SGPT, ALP, total bilirubin, creatinine, estimated CrCl)
- Urinalysis by dipstick within 2 days of Day 1 of each cycle. In case proteinuria ≥ 2+ is detected by the dipstick method, a 24-hour urine collection is needed to confirm renal function is within acceptable limits (< 1 g per day).
- Pregnancy test: only if clinically indicated.
- Tumor assessments will be performed every 2 cycles (± 7 days) during 2nd-line treatment, and then every 3 cycles (± 2 weeks) during 3rd-line and subsequent treatment, and at end of trial. Tumor assessment will not be repeated at the commencement of the subsequent line, if last tumour assessment was within 28 days (i.e. then the first assessment for PD 2 will be before Cycle 3 2nd-line; the first assessment for PD 3 before Cycle 4 3rd-line). The same imaging technique should be used throughout the trial. Evaluations will be done according to RECIST v1.1. The PD1 assessment will serve as baseline for determining PD2. The PD2 assessment will serve as baseline for determining PD3, etc. A CT/MRI scan of the brain should be repeated during the trial if CNS symptoms develop. Any response that is detected will be confirmed by a follow-up scan at least 4 weeks later.
- Adverse events: All grades of all AEs, SAEs and AEs of special interest will be recorded at every visit.
- Concomitant medications and treatment: only relevant medications (i.e. supportive treatment for SOC treatment) used to treat NSCLC and to treat medically significant

conditions and AEs are to be recorded (see Section 4.4). Radiotherapy and surgery should also be recorded.

- QoL (EORTC QLQ-C30/QLQ-LC13) will be assessed within 3 days prior to Day 1 of each cycle until Cycle 2 of 3rd-line treatment, then every 2nd cycle up to an including PD3 or until cessation of trial treatment, and then at trial termination.
- RCR sampling (optional) involves the collection of:
  - a non-genetic plasma samples (2 x 6 mL) every 4 cycles (12 weeks, ± 2 weeks) during treatment and at end of treatment. These samples can also be taken on Day 1 of the cycle immediately after the one specified in the table together with laboratory assessment samples. In that case, care must be taken that the RCR non-genetic blood sample is only drawn before any component of trial treatment is administered. Sampling will stop for patients continuing treatment beyond 4th-line.
- If the SOC agent needs to be discontinued due to toxicity or patient request:
  - patients in arm A should continue to receive bevacizumab until the occurrence of an unacceptable toxicity or until withdrawal of consent. No crossover is allowed.
  - an alternative SOC agent may be commenced.
- If any or all SOC agent(s) needs to be discontinued due to toxicity or due to the completion of the course of treatment, the patient should continue to receive bevacizumab until the occurrence of an unacceptable toxicity or until withdrawal of consent.

Post-therapy follow-up for patients who prematurely stop treatment:

Safety follow-up visit: 30 days (± 2 days) after the last dose of bevacizumab (Arm A) or SOC (Arm B), patients will undergo a safety follow-up assessment, including general physical examination, vital signs, ECOG PS, all AEs, all SAEs, all AEs of special interest, laboratory assessments, and concomitant medications and therapies. QoL will also be assessed.

PD follow-up visit (prior PD 3): Patients for whom trial treatment was stopped will visit every 12 weeks (± 2 weeks) (first visit will be 8 weeks after the safety follow-up assessment). Assessments will include general physical examination, vital signs, ECOG PS (until PD3), tumor assessment (until PD3), all related SAEs, all AEs of special interest for 6 months after drug cessation, and concomitant medications and therapies (to PD3).

Survival follow-up (post PD 3): Following the Safety-FU visit/PD-FU visits (see above, whichever occurs later), patients will be contacted every 12 weeks (± 2 weeks) until trial end in order to capture their survival status, and if applicable follow-up on related SAEs and AEs of special interest for 6 months after drug cessation.

End of trial (all patients):

End of trial visit: This visit will be at trial end with the exception of patients who die before trial end, withdraw consent to be followed up in the trial or are lost to follow-up.

Depending on the patient's status at the end of trial visit, assessments will consist of those specified for the respective visit. Example: A patient on treatment will be scheduled for various assessments, incl. a tumor assessment (if not performed within 28 days), whereas for a patient in survival FU who stopped bevacizumab 8 months prior only information about the potential death and related SAEs will be collected.

After study closure:

After study closure, the Sponsor should be notified if the investigator becomes aware of any death, serious adverse event, or other non-serious AEs of special interest occurring at any time after a patient has discontinued study participation regardless of the relationship to the study drug. The investigator is not required to actively monitor patients after the study has ended.

Table 1 Schedule of Assessments

	Pretreatment Baseline			Treatment Period					Follow up for patients stopping treatment prematurely			End of study
Cycle or interval	Screening within day 1 of cycle 1			Second-line prior to each cycle	PD 2	Third-line prior to each cycle[1]	PD 3	Fourth-line & beyond prior to each cycle[1]	Day 30 (± 2 days)	Every 12 weeks prior to PD3[20]	Every 12 weeks post PD3[20]	Study Termination[21]
	28 d	7 d										
Informed Consent	X		RANDOMIZATION		2nd PROGRESSION OF DISEASE		3rd PROGRESSION OF DISEASE					
Eligibility Criteria		X										
Demographics, Medical History, and Concurrent Illness	X											
Lung Cancer History[2]	X											
ECG	X			As clinically indicated		As clinically indicated		As clinically indicated	As clinically indicated			As clinically indicated
Left Ventricular Ejection Fraction				As clinically indicated		As clinically indicated		As clinically indicated	As clinically indicated			As clinically indicated
Physical Exam and Vital Signs[4]	X			X		X		X	X	X		X
ECOG PS		X		X		X		X	X	X		X
Hematology[5]		X		X		X		X	X			X
Coagulation[6]		X		As clinically indicated[d]		As clinically indicated[d]		As clinically indicated[d]	As clinically indicated[d]			As clinically indicated[d]
Blood Chemistry[7]		X		X		X		X	X			X
Urinalysis[8,9]		X		X		X		X	X			X
Pregnancy Test[3]		X		As clinically indicated[d]		As clinically indicated[d]		As clinically indicated[d]	As clinically indicated[d]			As clinically indicated[d]

	Pretreatment Baseline			Treatment Period					Follow up for patients stopping treatment prematurely			End of study
Cycle or interval	Screening within day 1 of cycle 1			Second-line prior to each cycle	PD 2	Third-line prior to each cycle[1]	PD 3	Fourth-line & beyond prior to each cycle[1]	Day 30 (± 2 days)	Every 12 weeks prior to PD3[20]	Every 12 weeks post PD3[20]	Study Termination[21]
	28 d	7 d										
Tumor Assessment[10]	X		RANDOMIZATION	Every 2 cycles[10]	PROGRESSION OF DISEASE	Every 3 cycles[10]	PROGRESSION OF DISEASE	Every 3 cycles[10]		X		x
AEs, SAEs and AEs of special interest[11]	Intervention related SAEs only			Continuously		Continuously		Continuously	All AEs	Ongoing and related AEs, related SAEs and AEs of special interest		X
SOC ± Bevacizumab[12]				X[13]		X[14]		X[15]				X
Concomitant Relevant Medication & Therapy (incl. Radiotherapy & Surgery)				X		X		X	X	X		X
Survival	X			Continuously		Continuously		Continuously	Continuously			X
QoL[16]		X		X[17]		X		Every 2 cycles	X	X		X[17]
Biomarker DNA, if applicable[18]	X											
Biomarker non-DNA, if applicable[19]		X		Every 4 cycles		Every 4 cycles		Every 4 cycles	X			
Biomarker Tissue, if applicable[22]	X											

Footnotes:

1. For the purposes of scheduling assessments and visits for 3rd-line treatment and beyond (as the SOC treatment may not be based on a 3-week cycle), "cycles" are based on bevacizumab scheduling for Arm A. In Arm B, patient's visits should occur Q3W if possible, regardless of the SOC treatment schedule.
2. Histologically or cytologically (sample to be obtained by biopsy or bronchoscopy, no rebiopsy is needed at PD1) confirmed predominantly non squamous locally recurrent or metastatic NSCLC.
3. Pregnancy test requirement details see Section 5.4.1
4. Includes weight and blood pressure. Height is also measured, but only at screening. Subsequent physical examinations should be symptom directed.
5. Hematology (hemoglobin, hematocrit, RBC, WBC with differential, platelet count) within 7 days prior to Cycle 1, within 3 days prior to subsequent cycles, and to be available before administration of trial treatment. All abnormalities should be recorded in the eCRF as AE.
6. INR and aPTT or equivalent test at trial entry and when clinically indicated, except that patients receiving full doses of coumarin derivatives at baseline should have two consecutive INR measurements 1–4 days apart. Coagulation tests for the patient on (prophylactic or full dose) anticoagulation treatment should be done at least before start of every SOC cycle. All abnormalities should be recorded in the eCRF as AE.
7. Chemistry (including total protein [or albumin only], AST/SGOT, ALT/SGPT, ALP, total bilirubin, creatinine): within 7 days prior to Cycle 1, within 3 days prior to subsequent cycles, and to be available before administration of trial treatment. All abnormalities should be recorded in the eCRF.
8. Urinalysis: within 7 days prior to Cycle 1, within 3 days prior to subsequent cycles, and to be available before administration of trial treatment. All abnormalities should be recorded in the eCRF.
9. Dipstick for proteinuria to be performed within 2 days prior to bevacizumab administration unless a 24-hour urine collection has been performed as specified in the protocol Section 6.1.1.4.
10. Tumor assessments: the same imaging method (CT/MRI) must be used for a patient throughout the trial) every 2 cycles (± 7 days) from date of randomization until 2nd progression of disease, after which tumor assessments should be performed every 3 cycles (± 2 weeks). Tumor assessments are performed at PD. Tumor assessment will not be repeated at the commencement of the subsequent line/end of treatment if last tumour assessment was within 28 days. Section 5.3.1
11. All AEs, SAEs, and AEs of special interest must be recorded throughout the trial. After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in). For follow-up of AEs see protocol Section 7.1.2 for details. Events unrelated to trial drug are to be followed for 30 days after last bevacizumab treatment. AE of special are to be reported for 6 months after last treatment. Related SAEs are to be reported indefinitely. At the safety follow-up visit, the investigator should instruct each patient to report to the investigator any subsequent adverse events. After study closure, the Sponsor should be notified if the investigator becomes aware of any death, SAE or other non-serious AEs of special interest occurring at any time after a patient has discontinued study participation regardless of the relationship to the drug. The investigator is not required to actively monitor patients after the study has ended.

12. No cross over of bevacizumab is allowed.
13. 2nd-line standard or care (SOC) treatment includes erlotinib, docetaxel or pemetrexed. Cycles are 21 days (± 3 days).
14. Choice and schedule of 3rd-line SOC treatment is at the discretion of the investigator based on local practice. No cross over of bevacizumab is allowed. Bevacizumab cycles are 21 days (± 3 days).
15. Choice of fourth and later line SOC treatment and schedule is at the discretion of the investigator based on local practice. Bevacizumab administration (including as monotherapy) may continue if patients benefit. No cross over of bevacizumab is allowed. Bevacizumab cycles are 21 days (± 3 days).
16. During the treatment period, QoL questionnaires must be completed by the patient before receiving trial treatment.
17. Not to be repeated if within 1 week of the last QoL assessment/sample.
18. Optional; requires additional, written informed consent. One 6 mL whole blood RCR sample (in K3 EDTA) for genetic analyses will be collected before treatment start.
19. Optional; requires additional, written informed consent. Two RCR blood plasma samples (in EDTA) with 6 mL will be taken before treatment start, after every 4 cycles (12 weeks (± 2 weeks)) during treatment, and at the end of treatment. Please note that biomarker sampling will stop for subjects who continue beyond 4th-line treatment.
20. First visit will be 8 weeks (± 2 weeks) after the 30 day visit, thereafter every 12 weeks (± 2 weeks).
21. Maximum number of applicable assessments are indicated. (i.e. for a patient still on trial treatment at the end of trial. Patients in other follow-up will have assessments as specified in their respective follow up visit.)
22. Optional; requires additional, written informed consent. Twenty slides of formalin fixed tumor tissue embedded in paraffin blocks will be collected for all consenting patients; Section 5.4.2

PART I: TRIAL DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND

1.1.1 Non-squamous non-small cell lung cancer

Lung cancer is the most common cause of cancer death worldwide, accounting for up to 18% of cancer-related deaths.[1] NSCLC comprise 80% of reported lung cancer cases.[2] Indeed, the majority of new cases of lung cancer are advanced NSCLC.[3] Due to late diagnosis, only a small proportion of NSCLC cases are operable as over 60% of patients present with advanced stages of the disease.[4] In comparison with other solid tumors, the objective response and OS rates in patients with advanced NSCLC are low: five-year survival rates for stage IIIB inoperable disease are less than 10%, decreasing to less than 2% in disease stage IV.[5]

For this population of patients in whom treatment is mainly palliative, the main goal is to achieve symptom control and prolong OS.[6] Standard of care for patients with locally advanced or metastatic NSCLC is platinum-based doublet chemotherapy.[7] Doublet chemotherapy has been found to be superior to single-agent chemotherapy,[8] with cisplatin-based treatment the current reference treatment for patients with advanced NSCLC. However, no doublet combination has been proven to be clinically superior to the others.[9-12] Current data suggest that chemotherapy has reached a therapeutic plateau, conferring no improvements in survival despite the availability of new combinations of cytotoxic agents.[11,13] In addition, there are only limited treatment options for those who fail 1st-line chemotherapy. Overall, the survival outcomes for NSCLC patients with chemotherapy remain poor, with 5-year survival rate of only 33% in patients with operable disease.[14]

Recent trials have shown that patients with advanced NSCLC can benefit from 2nd-line treatment.[6] However, therapeutic options in this setting are fairly limited. Currently, docetaxel and pemetrexed are two widely used chemotherapy agents approved for use as 2nd-line treatment.[15] Further compounding the problem, there also remains a large population of patients who do not benefit from these agents or are too unfit to receive them.[6]

In addition to chemotherapy, drugs that target the epidermal growth factor receptor (EGFR) play an important role in advancing NSCLC treatment and improving patient outcomes.[16] Erlotinib has been approved in the US and Europe for 2nd-line treatment of NSCLC.[16] Results from a pivotal Phase III trial in patients with stage IIIB/IV NSCLC who had previously received chemotherapy showed that the use of erlotinib resulted in a 42.5% improvement in mean OS compared to placebo.[17] Erlotinib acts via a different mechanism of action than chemotherapy agents, providing an important treatment alternative for those patients who do not benefit from standard chemotherapy.

The European SELECTTION[59] observational study in over 1000 patients, found that docetaxel, pemetrexed and Erlotinib are given to 90% of patients in second line treatment for NSCLC.

1.1.2 Bevacizumab

Please refer to the current version of the bevacizumab Investigator's Brochure for further details.

Bevacizumab is a recombinant humanized monoclonal antibody to Vascular Endothelial Growth Factor (VEGF) composed of human IgG1 framework regions and antigen-binding complementary determining regions from a murine monoclonal antibody (muMAb VEGF A.4.6.1) that blocks the binding of human VEGF to all VEGF-A receptors.[18]

Bevacizumab recognizes and neutralizes isoforms of VEGF with a K_d of approximately 8 x 10^{-10} M. It does not recognize other peptide growth factors tested (fibroblast growth factor, epidermal growth factor, hepatocyte growth factor, platelet-derived growth factor and nerve growth factor). It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment. Additional anti-tumor activity may be obtained via the effects of bevacizumab on tumor vasculature, interstitial pressure and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells.[19] In addition, bevacizumab showed synergistic antiangiogenic activity with docetaxel, as assessed by endothelial cell proliferation and tubule formation, *in vitro*.[20]

Anti-VEGF antibodies have shown benefit when combined with chemotherapy in preclinical models of different tumor types. Bevacizumab can block the growth of a number of human cancer cell lines grown in nude mice, including metastatic colorectal cancer (mCRC), non-squamous NSCLC, metastatic or locally recurrent breast cancer (BC), prostate cancer, head and neck cancer, metastatic renal cell carcinoma (mRCC) and ovarian cancer.[21-24]

Bevacizumab has been tested in many phase I to IV studies in a variety of solid tumors as monotherapy and in combination with chemotherapy. The combination of bevacizumab with chemotherapy improves PFS and/or OS in mCRC,[25-28] non-squamous NSCLC,[29] metastatic breast cancer (mBC),[30,31] mRCC,[32,33] and ovarian cancer.[34] As of November 2011, bevacizumab has been approved in more than 100 countries worldwide (including the member states of the European Union (EU), and the United States of America) for the treatment of some forms of colorectal, breast, renal, lung and brain cancers. As of April 2011, over 1,000,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials in different indications. Bevacizumab is under investigation for the treatment for multiple other oncology indications including cervical cancer, sarcomas and Non-Hodgkin's lymphoma.

1.1.2.1 Bevacizumab in non small-cell lung cancer

Two phase III clinical trials (E4599 and AVAiL) have demonstrated that 1st-line bevacizumab in combination with platinum-based chemotherapy significantly improves clinical outcomes in patients with advanced or recurrent NSCLC.[29,35] In

E4599 (NCT00021060), the hazard ratios (HRs) for PFS and OS were 0.66 ($p < 0.001$) and 0.79 ($p = 0.003$), respectively, for bevacizumab-based treatment *vs* chemotherapy alone.[29] Furthermore, among patients with adenocarcinoma histology in a retrospective analysis of E4599, bevacizumab-based treatment improved median OS to 14.2 months (HR 0.69).[36] In the AVAiL trial (BO17704), PFS (the primary endpoint) was significantly improved with bevacizumab-based treatment *vs* chemotherapy plus placebo (HR 0.75, $p = 0.003$ and HR 0.82, $p = 0.03$ for bevacizumab 7.5 mg/kg Q3W and 15 mg/kg Q3W, respectively).[35,37] While the median OS in AVAiL was greater than 13 months in all treatment groups, there was no difference in OS between the bevacizumab groups and the placebo group (HR 0.93, $p = 0.420$ and HR 1.03, $p = 0.761$ for bevacizumab 7.5 mg/kg and 15 mg/kg, respectively). PFS was significantly prolonged; the hazard ratios for PFS were 0.75 (median PFS, 6.7 vs. 6.1 months for placebo; $p = 0.003$) in the low-dose group and 0.82 (median PFS, 6.5 vs. 6.1 months for placebo; $p = 0.03$) in the high-dose group. Objective response rates (ORRs) were 20.1%, 34.1%, and 30.4% for placebo, low-dose bevacizumab, and high-dose bevacizumab plus CG, respectively. Duration of follow-up was not sufficient for OS analysis. Incidence of Grades ≥ 3 AEs was similar across arms. Grade ≥ 3 pulmonary hemorrhage rates were ≤ 1.5% for all arms despite 9% of patients receiving therapeutic anticoagulation.

1.1.2.2 Treatment in multiple lines with bevacizumab

In the BRiTE tumor registry, patients with mCRC were followed in a large, prospective, observational trial to assess outcomes based on chemotherapy regimens and bevacizumab exposure.[38] Data from the BRiTE registry suggested that patients who had progressed on 1st-line treatment with bevacizumab had a statistically significant improvement in survival beyond first progression if they continued to receive bevacizumab with other chemotherapy compared with patients who received other chemotherapy alone in subsequent lines. Patients receiving no treatment had a median OS of 12.6 months, patients who did not receive bevacizumab post-PD had a median OS of 19.9 months and patients receiving bevacizumab post-PD had a median OS of 31.8 months (HR: 0.48; 95% CI: 0.41-0.57; $p < 0.001$).

A second tumor registry (ARIES) has shown similar outcomes,[39] patients with mCRC who initiated or continued treatment with bevacizumab at first progression had a significantly longer median survival post first progression than those patients who received chemotherapy or biological treatment alone (16.1 vs 9.5 months; $p < 0.001$). In addition, analysis of outcomes in patients enrolled in 2nd-line and received bevacizumab as 2nd-line treatment showed that survival was longer in those patients who had received bevacizumab as part of their 1st-line treatment compared with those patients who initiated bevacizumab in the 2nd-line (20.4 vs 17.1 months).

1.1.2.3 Safety of bevacizumab

In the Phase III trial programme conducted across several tumor types, bevacizumab has demonstrated a favourable safety profile with a low incidence

of grade 3 or 4 AEs. Some specific side effects associated with the use of bevacizumab (either alone or in combination with chemotherapy) are as follows (see also Section 6.1.1):

- Hypertension
- RPLS
- Proteinuria
- Hemorrhage
- Thromboembolism
- Gastrointestinal perforation
- Fistulae
- Wound-healing complications
- CHF

Phase II and III clinical trials have demonstrated a manageable AE profile for bevacizumab in non-squamous NSCLC. In a phase II trial, pulmonary bleeding events appeared to be more common in patients with squamous cell lung cancer.[6] The subsequent exclusion of patients with squamous cell histology from bevacizumab clinical trials in NSCLC significantly reduced the incidence of grade ≥ 3 pulmonary bleeding, which occurred in 1.9% of bevacizumab-treated patients in E4599, and in 1.5% and 0.9% of patients receiving bevacizumab 7.5 mg/kg and 15 mg/kg, respectively, in AVAiL. In E4599 and AVAiL, the incidence of hypertension, proteinuria and bleeding were modestly higher in the bevacizumab arms relative to the control arms.[29, 35]

SAiL (MO19390) was an international open-label, multicenter, single-arm phase IV trial conducted to assess the safety of 1st-line bevacizumab combined with standard chemotherapy regimens in clinical practice.[40] The SAiL trial extended the clinical experience of bevacizumab by allowing the use of chemotherapy regimens other than those investigated in the pivotal trials, and by including patients who have an ECOG PS of 2. 2,212 patients in the intent-to-treat population of had previously untreated locally advanced, metastatic or recurrent non-squamous NSCLC, and received bevacizumab (7.5 or 15 mg/kg i.v. every 21 days) plus standard chemotherapy for up to 6 cycles, followed by single-agent bevacizumab until PD. Clinically significant (grade ≥ 3) AEs of special interest were relatively uncommon: bleeding (3.6%), pulmonary hemorrhage (0.7%), hypertension (5.7%), proteinuria (3.0%) and thromboembolism (7·8%). Fifty-seven patients (2.6%) died due to an AE of special interest, most commonly thromboembolism (1.2%) and bleeding (0.8%). The most common grade ≥ 3 serious AEs deemed by investigators to be associated with bevacizumab were pulmonary embolism (1.3%) and epistaxis, neutropenia, febrile neutropenia and deep vein thrombosis (all of which occurred in 0.6%). Bevacizumab was permanently discontinued for 8.2% of bleeding events and 3.9% of hypertension events. No new safety signal was reported.

Patients with NSCLC and brain metastases have previously been excluded from trials of bevacizumab because of suspected risk of CNS hemorrhage. The phase II trial, AVF3752g (PASSPORT), specifically addressed bevacizumab safety (incidence of grade ≥ 2 CNS hemorrhage) in patients with NSCLC and previously treated brain metastases.[41] Of 106 safety-evaluable patients, median on-trial duration was 6.3 months (range, 0 to 22 months), with a median of five bevacizumab cycles (range, one to 17), and no reported episodes of grade ≥ 2 CNS hemorrhage (95% CI, 0.0% to 3.3%).

For information regarding other side effects associated with the use of bevacizumab (either alone or in combination with chemotherapy), please refer to the current version of the Investigator's Brochure.

1.1.3 Erlotinib

Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the EGFR. Specificity of inhibition with regard to other tyrosine kinase receptors has not been fully characterized.

1.1.3.1 Clinical activity of erlotinib in NSCLC

Erlotinib is indicated for:

- Treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen

  The efficacy and safety of single-agent erlotinib was assessed in a randomized, double blind, placebo-controlled trial in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen.[17] Patients were randomized 2:1 to receive erlotinib 150 mg or placebo orally once daily until PD or unacceptable toxicity. There was a statistically significant and clinically meaningful prolongation of survival in patients treated with erlotinib. There was a 42.5% improvement in median OS in the erlotinib arm: median OS was 6.7 and 4.7 months for the erlotinib and placebo groups, respectively ($p = 0.002$). Tumor response was significantly higher with erlotinib (8.9% vs. 0.9%, $p < 0.001$); the duration of response was also longer with erlotinib (34.3 vs 15.9 weeks). The survival benefit of erlotinib was also seen in those patients that did not show an objective tumor response. In the subset of patients whose best response was stable/progressive disease (SD/PD), those treated with erlotinib showed a median survival time of 8.3 months, compared to 6.8 months for those on placebo (HR 0.82; 95% CI: 0.68-0.99; $p = 0.037$). Erlotinib conferred OS benefits regardless of age, gender, ethnicity, smoking status, ECOG PS, or tumor histology.

- Maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based 1st-line chemotherapy;

- Erlotinib is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations

1.1.3.2 Safety of erlotinib

The most frequently-reported AEs associated with single-agent erlotinib are rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache. The most common adverse reactions (> 20%) in 2nd-line NSCLC are rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, infection and vomiting. Laboratory abnormalities, primarily involving changes in liver function tests (elevation of ALT, AST and/or bilirubin) are less frequently observed with single-agent erlotinib.

The special warnings and precautions for use in the erlotinib Summary of Product Characteristics (SmPC) (see also Section 7.3.2) include the following:

- Interstitial lung disease
- Acute and chronic renal failure
- Hepatic failure and hepatorenal syndrome
- Gastrointestinal perforation
- Bullous and exfoliative skin disorders
- Myocardial infarction/ischemia
- CVAs
- Microangiopathic hemolytic anemia with thrombocytopenia
- Corneal perforation and ulceration
- INR elevations and bleeding events, some associated with concomitant warfarin administration

1.1.3.3 Bevacizumab in combination with erlotinib

The BETA trial (OSI3364g) was a Phase III, double-blind trial that evaluated the efficacy of erlotinib with bevacizumab or placebo as 2nd-line treatment in 636 patients with advanced NSCLC.[42] The addition of bevacizumab to erlotinib did not result in an increased OS, but did improve investigator-assessed PFS (HR 0.62, $p < 0.001$). Bevacizumab did not increase the proportion of patients with grade ≥ 3 hemorrhage (2.6% vs. 2.2%), but was associated with more arterial thromboembolic events (3.2% vs. 0.3%) and with more rash (15.7% vs. 6.1%).

The ATLAS study (n = 768) was a randomized, placebo-controlled trial that evaluated bevacizumab 15 mg/ kg Q3W with or without erlotinib 150 mg daily following 4 cycles of bevacizumab + platin-containing doublet chemotherapy in patients with Stage IIIb/IV NSCLC.[43] The trial was stopped at second interim analysis because the study met its primary endpoint of improving PFS, which was 4.8 months for bevacizumab + erlotinib compared with 3.7 months for bevacizumab + placebo (HR = 0.71, 95% CI: 0.58–0.86, p = 0.006). The safety profile for bevacizumab + erlotinib was consistent with known profiles for

bevacizumab and for erlotinib. The most frequently reported Grade 3-4 AEs were rash and diarrhea (recognized erlotinib toxicities), both of which had a higher incidence in the bevacizumab + erlotinib arm (10.4% vs. 0.5%; 9.3% vs. 0.8%, respectively). AEs that led to death occurred in 1.1% of patients in the bevacizumab + placebo arm and 2.2% in the bevacizumab + erlotinib arm. Grade 5 AEs of interest to bevacizumab in the bevacizumab + placebo arm were CHF (1 patient) and infection (1 patient) and in the bevacizumab + erlotinib arm were cardiovascular events other than hypertension (2 patients), arterial thromboembolism (1 patient) and venous thromboembolism (1 patient).

1.1.4 Docetaxel

Docetaxel disrupts the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells.

1.1.4.1 Clinical activity of docetaxel in NSCLC

Docetaxel is indicated for:

- single agent for locally advanced or metastatic NSCLC after platinum therapy failure

  Two randomized, controlled trials (Table 2) established that a docetaxel dose of 75 mg/m^2 was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy.[44,45] In TAX317, patients were initially randomized to docetaxel 100 mg/m^2 or best supportive care (BSC), but early toxic deaths at this dose led to a dose reduction to docetaxel 75 mg/m^2. A total of 104 patients were randomized in this amended trial to docetaxel 75 mg/m^2 or best supportive care. In TAX320, 373 patients were randomized to docetaxel 75 mg/m^2 or control (vinorelbine or ifosfamide). Forty percent of the patients in this trial had a history of prior paclitaxel exposure.

- with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC.

Table 2 Docetaxel as second-line treatment of NSCLC

	TAX317[44]			TAX320[45]		
	Docetaxel 75 mg/m^2	Control BSC	P value	Docetaxel 75 mg/m^2	Control VRB or IF	P value
N	55	49		125	123	
Patient population	• locally advanced or metastatic NSCLC • prior platinum-based chemotherapy • no prior taxane • ECOG PS ≤ 2			• locally advanced or metastatic NSCLC • prior platinum-based chemotherapy • ECOG PS ≤ 2		
Overall survival	RR 0.56 (0.35, 0.88)		0.01	RR 0.82 (1.06)		0.13
Median months	7.5	4.6	< 0.05	5.7	5.6	ns
TTP (weeks)	12.3	7.0	< 0.05	8.3	7.6	ns
Response rate (%)	5.5	..	..	5.7	0.8	..

Abbreviations: BSC, Best supportive care; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IF, ifosfamide; ns = not significant; NSCLC, non small-cell lung cancer; RR risk ratio; VRB, vinorelbine.

1.1.4.2 Safety of docetaxel

The special warnings and precautions for use in the docetaxel Summary of Product Characteristics (SmPC) (see also Section 7.3.3) include the following:

- Hypersensitivity
- Neutropenia and febrile neutropenia
- Thrombocytopenia
- Hepatic impairment
- Acute myeloid leukemia and myelodysplasia
- Localized erythema of the extremities with edema followed by desquamation
- Fluid retention
- Severe neurosensory symptoms (paresthesia, dysesthesia, pain)

1.1.4.3 Bevacizumab in combination with docetaxel

In a phase 2 trial, 40 patients with advanced NSCLC received bevacizumab (15 mg/kg) docetaxel (75 mg/m^2) and carboplatin (AUC 6) Q3W.[46] Patients received a median 6 cycles of bevacizumab for induction and 2 cycles for maintenance. The trial showed encouraging activity (median PFS was 7.9 months, median OS

was 16.5 months and overall response rate of 53%). Grade ≥ 3 AEs included febrile neutropenia (10%), infections (13%), bleeding (13%), thrombotic events (13%), hypertension (5%), bowel perforation (5%), and proteinuria (3%).

Bevacizumab in combination with docetaxel (or paclitaxel) is indicated for 1st-line treatment of patients with metastatic breast cancer in the EU. Please refer to the investigator brochure for more information regarding the established safety profile of bevacizumab with docetaxel in the BO17708 (AVADO) trial.

1.1.5 Pemetrexed

Pemetrexed is a pyrimidine-based folic acid analogue that inhibits multiple folate-dependent enzymes (thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl-transferase) crucial in the *de novo* biosynthesis of thymidine and purine nucleotides.

1.1.5.1 Clinical activity of pemetrexed in NSCLC

In Europe, the European Medicines Agency (EMA) has approved the use of pemetrexed in lung cancer patients and is indicated for:

- Use as monotherapy for 2nd-line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology.
- 571 patients with NSCLC previously treated with chemotherapy were randomly assigned to pemetrexed and docetaxel. Median survival time was 8.3 for pemetrexed versus 7.9 months for docetaxel and median PFS was 2.9 months in each arm. Patients receiving docetaxel were more likely to have grade 3 or 4 neutropenia (40.2% vs. 5.3%; $p < 0.001$), febrile neutropenia (12.7% vs. 1.9%; $p < 0.001$), neutropenia with infections (3.3% vs. 0.0%; $p < 0.004$), hospitalizations for neutropenic fever (13.4% vs. 1.5%; $p < 0.001$), hospitalizations due to other drug related adverse events (10.5% vs. 6.4%; $p < 0.092$), use of granulocyte colony-stimulating factor support (19.2% vs. 2.6%, $p < 0.001$) and all grade alopecia (37.7% vs. 6.4%; $p < 0.001$) compared with patients receiving pemetrexed.[47]
- Use in combination with cisplatin as 1st-line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology and
- Use as monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy.

1.1.5.2 Safety of pemetrexed

The special warnings and precautions for use in the pemetrexed SmPC (see also Section 7.3.4) include the following:

- Bone marrow suppression (neutropenia, thrombocytopenia, anaemia, or pancytopenia). Myelosuppression is usually the dose-limiting toxicity (DLT).

- Skin reactions, which can be reduced by pre-therapy with dexamethasone (or equivalent).
- Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. An insufficient number of patients have been studied with CrCL < 45 mL/min. The use of pemetrexed in patients with CrCl < 45 mL/min is not recommended.
- Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent.

1.1.5.3 Bevacizumab in combination with pemetrexed

A phase II trial (N = 48) has evaluated efficacy and safety of pemetrexed and bevacizumab as 2nd-line treatment of NSCLC.[48] Median PFS was 4 months. Median OS was 8.9 months. Grade 3+ and 4+ AEs occurred in 32 (67%) and 10 (21%) patients respectively. The most common (occurring in 10% or more of patients) grade 3/4 non-hematologic AEs were fatigue (13%), dyspnea (10%), and thrombosis (10%), and grade 3/4 hematologic AEs were neutropenia (19%), leukopenia (17%), and lymphopenia (13%).

A phase II study (N = 69 patients enrolled), investigating pemetrexed/oxaliplatin plus bevacizumab, followed by maintenance bevacizumab, as first-line therapy for advanced non-squamous NSCLC, showed encouraging activity (median PFS was 7.8 months, median OS was 16.7 months and disease control rate of 84%) with an acceptable toxicity profile.[49]

A phase II study AVF3075s (N = 50 patients), investigating pemetrexed/carboplatin plus bevacizumab, followed by maintenance pemetrexed and bevacizumab, as 1st-line therapy for advanced non-squamous NSCLC, showed encouraging activity (median PFS was 7.8 months, median OS was 14.1 months and overall response rate of 55%) with an acceptable toxicity profile.[50]

AVAPERL1 (MO22089), a multicentre, international phase III trial, investigated whether adding pemetrexed to bevacizumab maintenance further improves clinical outcomes over bevacizumab alone following Q3W induction with bevacizumab 7.5 mg/kg plus cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2. 376 patients were allocated to induction treatment; 125 and 128 were randomized to the bevacizumab and bevacizumab plus pemetrexed continuation maintenance arms, respectively. At a median follow-up of 10.9 months, PFS from induction was significantly improved in the bevacizumab + pemetrexed arm (10.2 vs 6.6 months; hazard ratio, 0.50 [95% confidence interval, 0.37–0.69]; $p < 0.001$).[62] Any-grade, grade ≥ 3, and serious adverse events were more frequent during bevacizumab + pemetrexed maintenance (37.6% and 17.6%, respectively) than in the BV-alone arm (21.7% and 13.3%, respectively). No new safety signals were observed.[51]

1.2 TRIAL RATIONALE

Advanced NSCLC remains a rapidly fatal disease where current chemotherapeutic options have only a modest positive impact. There is therefore a need to combine the best chemotherapy regimens with new targeted treatment, which has a different mode of action from chemotherapy and is also less toxic.

Failure of chemotherapy does not necessarily mean failure of antiangiogenic treatment with bevacizumab, a possibility supported by the BRiTE and ARIES registry data (see Section 1.1.2.2). This concept of bevacizumab treatment in multiple lines is prospectively being investigated in the mCRC setting by the ongoing randomized study ML18147 (see Investigator's Brochure for more details). The concept of treatment in multiple lines has been shown to be effective with the anti-HER2 antibody trastuzumab in patients with HER2-positive mBC.[52] Patients with NSCLC may similarly benefit from continued suppression of VEGF by bevacizumab with multiple consecutive SOC agents in an effort to prolong survival.

The current trial will evaluate whether bevacizumab in combination with SOC drugs as a 2nd-line and subsequent lines of treatment for NSCLC improves OS in patients who have progressed during or after 1st-line treatment with bevacizumab and platinum-containing doublet chemotherapy. Bevacizumab will be continued until unacceptable toxicity or withdrawal of consent (see Section 4.5 for other reasons of premature discontinuation).

As OS is sensitive to cross-over of patients to the experimental arm, no cross over is allowed during the trial duration The trial is designed to evaluate this treatment approach in a setting that reflects the reality of daily practice allowing the investigator a wide choice of approved SOC treatment.

1.2.1 Rationale for the optional biomarker Roche Clinical Repository (RCR)

It is the aim of the RCR program to elucidate the roles of VEGF, the VEGF receptor family, and other angiogenic factors and their association to response to bevacizumab treatment (in terms of dose, safety and tolerability) and will help to better understand the pathogenesis, course and outcome of NSCLC and related diseases.

The results of the biomarker program in this trial will be used to further support findings whether these molecules might serve as biomarkers that relate to clinical outcome or side effects in patients with NSCLC. In addition, these specimens can be used to further investigate early, intermediate and late escape mechanisms related to bevacizumab and SOC treatment regimen. Pre-clinical and clinical studies have begun to shed light on the mechanisms of resistance to anti-angiogenic drugs and several hypotheses have been formed. One of the hypothesized mechanisms is upregulation of alternative pro-angiogenic signaling pathways, e.g. the FGF or angiopoietin pathway.[53, 52] Another mechanism could be that vascular progenitor cells and pro-angiogenic monocytes are recruited from the bone marrow by excretion of SDF1α.[53]

The biomarker program in this trial will allow further investigation of these preliminary markers in NSCLC. Exploratory genetic analyses on DNA samples of bevacizumab treated patients have recently shown several polymorphisms that suggest that germline SNPs in angiogenesis pathway may predict clinical outcome or hypertension.[55-57]

Samples of the current trial will also be used to further explore the value of these and potential other genetic markers in NSCLC.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To assess the efficacy of continuous bevacizumab treatment beyond PD1 as measured by OS.

2.2 SECONDARY OBJECTIVES

- To assess the efficacy as measured by rate of 6-, 12-, and 18-month OS as measured from randomization at PD1.
- To assess the efficacy as measured by PFS and TTP from randomization at PD1 to PD2 (PFS2, TTP2), and to PD3
- To assess the efficacy as measured by RR, disease control rates, and duration of response at PD2 and PD3.
- To assess the efficacy in the subgroup of adenocarcinoma patients.
- To assess the safety of bevacizumab treatment across multiple lines of treatment.

2.3 EXPLORATORY OBJECTIVES

- To assess QoL through multiple lines of treatment.
- To compare the efficacy between Asian and non-Asian patients.

2.4 EXPLORATORY OBJECTIVES: OPTIONAL BIOMARKERS

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

- Explore the correlation of biomarkers with RR, PFS and OS.
- Investigate early, intermediate and late escape mechanisms related to bevacizumab and SOC treatment regimen

- Explore the association of biomarkers with response and adverse reactions
- Develop biomarker assays and to establish the performance characteristics of these assays

3. TRIAL DESIGN

3.1 OVERVIEW OF TRIAL DESIGN

This is a two-arm, open-label, randomized, multicenter, phase IIIb trial (see Figure 1).

Patients randomized to Arm A will receive bevacizumab 7.5 mg/kg i.v. or 15 mg/kg i.v. on Day 1 every 21 days (± 3 days) from Cycle 1 until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first). The approved (per label) dose (7.5 or 15 mg/kg i.v.) and Q3W schedule of bevacizumab used during 1st-line and maintenance treatment should be the same dose and schedule administered to each patient during the study.

Patients randomized to Arm B will not receive bevacizumab.

All patients (Arm A and Arm B) will receive one of the following drugs as 2nd-line SOC treatment until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first):

- Erlotinib 150 mg daily taken on an empty stomach at least one hour before or two hours after the ingestion of food

or

- Docetaxel 60 or 75 mg/m^2 on Day 1 every 21 days (± 3 days).

or

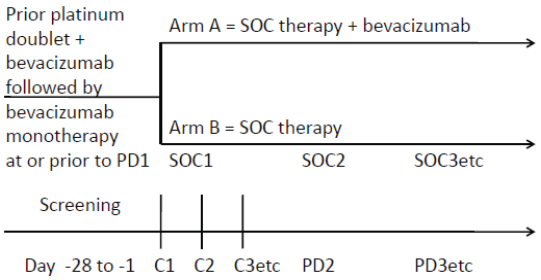
- Pemetrexed 500 mg/m^2 i.v. over 10 minutes on Day 1 every 21 days (± 3 days).

The 2nd-line SOC agent will be selected by the investigator prior to randomization.

Following PD2/3, 3rd- and 4th-line SOC treatment, respectively, will be chosen by the investigator according to local practice (Section 6.4).

SOC treatment can be altered or ceased or changed for PD or unacceptable toxicity. If SOC treatment is ceased permanently, bevacizumab treatment should continue provided there is no unacceptable toxicity related to bevacizumab or withdrawal of consent (see Section 4.5 for other reasons of premature discontinuation).

Figure 1 **Trial design**



Arm A: Patients will receive bevacizumab 7.5 mg/kg i.v. or 15 mg/kg i.v. on Day 1 every 21 days (± 3 days) in combination with SOC treatment from Cycle 1 until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first). The approved (per label) dose (7.5 or 15 mg/kg i.v.) and Q3W schedule of bevacizumab used during 1st-line and maintenance treatment should be the same dose and schedule administered to each patient during the study.

Arm B: Patients will receive SOC treatment without bevacizumab until unacceptable toxicity or withdrawal of consent (whichever occurs first).

SOC treatment can be changed for toxicity or progression of disease (PD).

3.1.1 Rationale for trial design

The primary aim of the trial is to assess the efficacy of bevacizumab when administered with SOC treatment for locally recurrent or metastatic non-squamous NSCLC in second and subsequent lines of therapy.

Several agents are indicated for the 2nd-line treatment of NSCLC, but no one agent has been proven to be superior to any other. Erlotinib, docetaxel and pemetrexed are widely used, approved drugs for the 2nd-line treatment of NSCLC. Therefore, patients will initiate erlotinib, docetaxel or pemetrexed in accordance with standard of care at each participating institution. The patients will be stratified according to planned treatment as investigators might plan 2nd-line treatment according to patient characteristics.

Tissue Sampling

In bevacizumab studies, biomarker analysis on tumor tissue showed that patients with Neuropilin (NRP) levels lower than the median appeared to experience a better bevacizumab treatment effect than those with high NRP levels.[60]

The regional differences in clinical outcome between Asian and non-Asian countries influenced additional biomarker analysis per region. Tumor NRP expression was significantly different between patients from Asian and non-Asian regions but is potentially confounded by the provision of tumor slides (93% in

Asia) rather than tumor blocks (83% in non-Asia) — since Immunohistochemistry (IHC) marker expression levels varied depending on the tumor tissue type. The apparent difference between 'Asia' and 'non-Asia' cannot be interpreted without further investigation.[61]

Therefore, only one type of material should be sent for IHC analysis in the current trial to prevent any bias in the analysis of tumor tissue markers. As tumor block shipping might give problems in some of the participating countries, slides is the preferred material for all consenting patients

3.1.2 Rationale for dose selection

The 21-day cycle with bevacizumab 7.5 mg/kg or bevacizumab 15 mg/kg has been widely used for the treatment of NSCLC. There is no evidence that either dose is more effective or safer than the other, with similar efficacy and safety in the AVAiL trial.[35]

Therefore, patients in MO22097 will receive bevacizumab 7.5 mg/kg or bevacizumab 15 mg/kg on Day 1 of each 21-day cycle. The approved (per label) dose (7.5 or 15 mg/kg i.v.) and Q3W schedule of bevacizumab used during 1st-line and maintenance treatment should be the same dose and schedule administered to each patient during the study.

Treatment duration and dose modifications for bevacizumab are described in Section 6.1.1.

Doses and dose modifications for the selected SOC treatment should be made according to local labels and local practice guidelines. Recommendations for doses and schedules of SOC treatment are listed in Section 6.3, and recommendations for dose modifications in this protocol are summarized in Section 6.5.

3.1.3 End of trial

End of trial is defined as the completion of observation period (i.e. when 416 deaths have been reported, or 60 months from study start, whichever occurs first.

Please see Section 5.5 for procedures for patients on trial drug at end of trial.

3.2 NUMBER OF PATIENTS

Approximately five hundred (500) patients will be recruited over a planned recruitment period of approximately 45 months.

3.3 CENTERS

This is a multi-national trial to be conducted in approximately 160 centers in approximately 25 countries.

4. TRIAL POPULATION

Under no circumstances are patients who are randomized in this trial permitted to be re-enrolled in this trial.

4.1 OVERVIEW

The trial population will comprise patients with locally recurrent or metastatic non-squamous NSCLC which has progressed beyond 1st-line treatment with bevacizumab plus a platinum doublet-containing chemotherapy regimen and a minimum of two cycles of bevacizumab (monotherapy) maintenance treatment, and who meet all inclusion criteria and none of the exclusion criteria listed below.

4.2 INCLUSION CRITERIA

1. Signed informed consent prior to initiation of any trial-specific procedure or treatment.
2. Age ≥ 18 years.
3. Able to comply with the protocol.
4. Histologically or cytologically (sample to be obtained by biopsy or bronchoscopy no rebiopsy is needed at PD1) confirmed non-squamous NSCLC with documented PD1 (locally recurrent or metastatic) per investigator assessment following 1st-line treatment with 4-6 cycles of bevacizumab plus a platinum doublet-containing chemotherapy regimen and a minimum of 2 cycles of bevacizumab (monotherapy) maintenance treatment prior to PD1.
5. No treatment interruption of bevacizumab treatment greater than 42 days defined as from start of 1st-line treatment to start of Cycle 1 of 2nd-line treatment.
6. Randomization within 4 weeks of PD1.
7. At least 1 unidimensionally measurable lesion meeting RECIST (v.1.1) criteria.
8. ECOG PS 0-2.
9. Life expectancy ≥ 16 weeks by investigator assessment.
10. Adequate hematological function:
    - ANC ≥ 1.5 x 10^9/L
    - Platelet count ≥ 100 x 10^9/L
    - Hemoglobin ≥ 9 g/dL (may be transfused to maintain or exceed this level).
11. Adequate liver function:
    - Total bilirubin < 1.5 x ULN
    - AST and ALT < 2.5 x ULN in patients without liver metastases; < 5 x ULN in patients with known liver metastases.
    - ALP < 2.5 x ULN (< 5 x ULN for patients with known liver involvement and < 7 x ULN for patients with known bone involvement).
12. Adequate renal function
    - Serum creatinine ≤ 1.25 x ULN or calculated creatinine clearance ≥ 50 mL/min

- Urine dipstick for proteinuria < 2+. Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate < 1 g of protein in 24 hours.

13. INR ≤ 1.5 and aPTT ≤ 1.5 x ULN within 7 days prior to randomization, unless there is prophylactic use of anti-coagulation. If local standards differ, equivalent coagulation tests may be used.
14. Patients with asymptomatic treated brain metastases are eligible for trial participation. Patients must complete treatment for brain metastases (radiotherapy or stereotactic radiosurgery), including steroids, at least 14 days prior to randomization. Treatment with anticonvulsants at the time of enrollment (i.e. ≥ 28 days) is allowed as long as the anti-convulsant is at a stable dose.
15. Female patients must not be pregnant or breast-feeding. Female patients of childbearing potential (defined as < 2 years after last menstruation or not surgically sterile) must use a highly effective contraceptive method (allowed methods of birth control, i.e. with a failure rate of less than 1 % per year, are implants, injectables, combined oral contraceptives, IUDs [only hormonspirals], sexual abstinence or vasectomized partner) during the trial and for a period of at least 6 months following the last administration of trial drug(s). Female patients with an intact uterus (unless amenorrhoeic for the last 24 months) must have a negative serum pregnancy test within 7 days prior to randomization into the trial.
16. Fertile male patients must agree to use a highly effective contraceptive method (allowed methods of birth control, i.e. with a failure rate of less than 1 % per year, female partner using implants, injectables, combined oral contraceptives, IUDs [only hormonspirals], sexual abstinence or prior vasectomy) during the trial and for a period of at least 6 months following the last administration of trial drug(s).

4.3 EXCLUSION CRITERIA

1. Mixed, non-small cell and small cell tumors or mixed adenosquamous carcinomas with a predominant squamous component.
2. EGFR-mutation-positive disease according to local laboratory testing. EGFR testing is not mandatory. In centers where this is not routinely done, patients with unknown EGFR mutation status are allowed to participate in this trial.
3. History of pulmonary hemorrhage/hemoptysis ≥ grade 2 (defined as bright red blood of at least 2.5 mL) within 3 months prior to randomization.
4. Surgery (including open biopsy), significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during trial treatment.
5. Minor surgery, including insertion of an indwelling catheter, within 24 hours prior to the first bevacizumab infusion.
6. Evidence of tumor invading a major blood vessel (e.g., pulmonary artery or superior vena cava) on imaging.

7. Radiotherapy to any site for any reason within 28 days prior to randomization. Palliative radiotherapy to bone lesions or the brain ≥ 14 days prior to randomization is allowed.
8. Current or recent (within 10 days prior to first dose of bevacizumab) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day), or current or recent (within 10 days prior to first dose of bevacizumab) use of full-dose (i.e. therapeutic dose) oral or parenteral anticoagulants or thrombolytic agent for therapeutic purposes. Prophylactic use of anticoagulants is allowed.
9. History or evidence of inherited bleeding diathesis or coagulopathy with a risk of bleeding.
10. Active gastrointestinal bleeding.
11. Inadequately controlled hypertension (blood pressure: systolic > 150 mmHg and/or diastolic > 100 mmHg) within 28 days prior to randomization or history of hypertensive crisis or hypertensive encephalopathy.
12. Clinically significant (i.e. active) cardiovascular disease (e.g. CVA or myocardial infarction within 6 months prior to randomization, unstable angina, CHF NYHA Class ≥ II, or serious cardiac arrhythmia – see Appendix 8), that is uncontrolled by medication or may interfere with administration of trial treatment.
13. Non-healing wound, active skin ulcer or untreated bone fracture.
14. History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to randomization.
15. Treatment with any other investigational agent within 28 days prior to randomization. Patients in the follow-up phase of 1st-line trials who fulfill all eligibility criteria may be enrolled in this trial if the 1st-line protocol allows bevacizumab-based treatment in the follow-up phase.
16. Known hypersensitivity to bevacizumab or any of its excipients, or any of the SOC drugs foreseen.
17. Malignancy other than NSCLC within 5 years prior to randomization, except for adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated with curative intent, and DCIS treated surgically with curative intent.
18. Evidence of any other disease, neurologic or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational or SOC drug used in this study or puts the patient at higher risk for treatment-related complications.

4.4 CONCOMITANT MEDICATION AND TREATMENT

All relevant concomitant medication(s) and treatments (i.e. supportive treatment for SOC treatment) used to treat NSCLC and to treat medically significant conditions and AEs, must be reported in the electronic case report form (eCRF).

In addition, all relevant diagnostic, therapeutic or surgical procedure performed during the trial period, should be recorded including the date, indication, description of the procedure(s), and any clinical findings.

All non-cancer therapies that the responsible physician feels are appropriate are allowed in the trial.

Patients should receive full supportive care during and after the administration of bevacizumab with or without SOC treatment. This includes transfusion of blood and blood products and/or the use of erythropoietin or G-CSF, antiemetics, antibiotics for infective complications and anti-hypertensives for the management of hypertension. Anaphylaxis precautions should be observed during administration of bevacizumab as per local practice.

The chosen 2nd-line SOC treatment will be administered according to local standards as outlined in Section 6.3.1 (erlotinib), Section 6.3.2 (docetaxel) and Section 6.3.3 (pemetrexed).

Any medication contraindicated when using bevacizumab and erlotinib or docetaxel or pemetrexed is not permitted and special warnings and precautions for use of erlotinib, docetaxel and pemetrexed should be observed (see Section 7.3). For premedication of docetaxel see Section 6.3.2, and for pemetrexed see Section 6.3.3.

Patients with full dose of anticoagulation agents at baseline for therapeutic use cannot be included in the study. Prophylactic use of anticoagulation at baseline and during study treatment for the maintenance of patency of permanent indwelling central venous access devices is permitted as well as prophylactic use of anticoagulation during study treatment for patients at high risk of venous thromboembolism providing that:

- Stable dosing of anticoagulants for at least two weeks has been achieved, INR or aPTT is within therapeutic limits (according to the medical standard in the institution)
- The patient must not have had any evidence of tumour invading major blood vessels on any prior CT scan.
- The patient has no evidence of CNS metastases

Therapeutic anticoagulation is allowed for treatment of grade 3 venous thromboembolism with onset after the start of the trial **after careful consideration of the benefit risk in selected patients as long as INR or aPTT is within therapeutic limits (according to the medical standard in the institution)**. For the management of patients that develop grade 3 or grade 4 venous thromboembolism please refer to Section 6.1.1.6.

Due to a possible risk of bleeding during treatment with bevacizumab, patients should not take more than 325 mg of aspirin daily (or more than 75 mg of clopidogrel daily) at least until discontinuation of bevacizumab treatment.

Treatment with concomitant, systemic anti-tumor agents not defined in this protocol as trial treatment is not allowed before 3rd-line treatment. Treatment with other concurrent investigational agents of any type is not allowed before 4th-line. See also Section 6.4.

4.4.1 Radiotherapy

Radiotherapy to any site for any reason within 28 days prior to randomization and palliative radiotherapy to bone lesions or the brain within 14 days prior to randomization are not allowed (Section 4.3).

During the trial:

- Patient can resume treatment with bevacizumab/SOC if palliative radiotherapy to bone lesions or to the brain was given during the trial if the treatment interruption with bevacizumab/SOC is ≤ 42 days (Section 6.1.1) and if last dose of palliative radiotherapy was 14 days prior to restarting bevacizumab/SOC.
- If the patient receives other radiotherapy, treatment with bevacizumab/SOC can only be restarted after discussion and approval of the Roche Medical Monitor or his/her designee

All radiotherapy must be reported in the electronic case report form (eCRF).

4.5 CRITERIA FOR PREMATURE WITHDRAWAL

Patients have the right to withdraw from trial treatment or from the trial at any time for any reason without affecting their right to an appropriate follow-up treatment.

Reasons a patient may discontinue **treatment** include, but are not limited to:

- Treatment failure (the investigator assesses SOC ± further VEGF inhibition with bevacizumab as futile)
- Adverse event [a]
- Patient request (withdrawal of consent for further treatment) [b]
- Investigator request (with detailed documentation of reasoning) [c]
- Protocol violation
- Patient non compliance
- Trial termination by the Sponsor [d]
- Death.

When a patient discontinues trial treatment or is withdrawn, the investigator will notify the Sponsor and, when possible, will perform the procedures indicated for the end of treatment visit.

Follow-up information will be obtained for patients who discontinue the treatment phase of the trial. See the flowcharts for procedures to be performed at end of treatment and follow-up visits in Table 1.

Patients may be discontinued from **the trial** for the following reasons only:

- Patient request (withdrawal of consent for further FU, including survival FU) [b]
- Trial termination by the Sponsor [d]
- Lost to follow-up [e]
- Death.

a. If the reason for removal of a patient from the trial is an AE, the principal specific event will be recorded on the eCRF. The patient should be followed until the AE has resolved, if possible. If the AE is deemed serious, it must be reported via the electronic SAE pages of the eCRF no more than 24 hours after learning of the event.

b. In the case that the patient decides to prematurely discontinue, he/she should be asked if he/she can still be contacted for further information i.e. the investigator needs to clarify the extent of withdrawal of consent (to treatment or to by followed up in the trial). The outcome of that discussion should be documented in both the medical records and in the eCRF. Consent withdrawal by the patient must be documented in writing by the patient or his/her legal representative.

c. When applicable, patients should be informed of circumstances under which their treatment may be terminated by the investigator (e.g. treatment failure, adverse event) without the patient's consent.

d. The Sponsor has the right to terminate the trial at any time. Reasons may include, but are not limited to, the following: The incidence or severity of AE in this or other studies indicates a potentially negative benefit risk ratio for patients; patient enrollment is unsatisfactory; data recording is inaccurate or incomplete. See also Section 14

e. An effort must be made to determine why a patient fails to return for the necessary visits or is dropped from the trial. This information will be recorded in the medical record and on the patient's eCRF. Lost to follow-up is defined as 3 failed attempts by phone followed by one attempt of sending a letter that requires signature.

Patients withdrawn from trial treatment or from the trial will not be replaced, regardless of the reason for withdrawal.

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

4.5.1 Withdrawal of patients from the Roche Clinical Repository (RCR)

Patients who gave consent to provide RCR specimens have the right to withdraw their specimen from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his/her specimen(s), the investigator must inform the Roche monitor or designee in writing of the patient's wishes using the

RCR Patient Withdrawal Form. If requested prior to database closure, the date of withdrawal from RCF will be captured in the patient's eCRF. Upon processing the withdrawal request, of this patient, no further analysis will be performed on his/her specimens and any remaining RCR specimens will be destroyed. A patient's withdrawal from the main trial does not, by itself, constitute withdrawal of the specimen from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute a withdrawal from the main trial.

4.6 REPLACEMENT POLICY (ENSURING ADEQUATE NUMBERS OF EVALUABLE PATIENTS)

4.6.1 For patients

Patients randomized into the trial will not be replaced.

4.6.2 For centers

A center may be replaced for, though not limited to, the following administrative reasons:

- Excessively slow recruitment (e.g. no patients enrolled within 3 months following site initiation without successful corrective actions to improve enrollment rate).
- Poor protocol adherence and/or repeated protocol violations.
- Repetitive late / inaccurate clinical data entry or failure to resolve data queries in the eCRFs.
- Non-compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Please refer to Table 1 detailing the schedule of assessments.

5.1 SCREENING EXAMINATION AND ELIGIBILITY SCREENING FORM

All patients must provide written, informed consent before any trial-specific assessments or procedures are performed (and separate informed consent for optional biomarker assessments).

A screening examination ("baseline") should be performed between 28 days and 1 day before the first dose of treatment (for specific timelines see Table 1), which will include the following procedures (unless the procedures have already been conducted during this time period as part of the patient's routine clinical care:

- Eligibility (inclusion and exclusion criteria, as listed in Section 4.2 and Section 4.3, respectively)
- Demographics (including ethnicity), complete medical history, concurrent illnesses

- Medical history including demographics, previous and current diseases
- Lung cancer history to include smoking history (current or past smoker status, number of pack-years), prior surgery, radiotherapy, chemotherapy and other anti-tumor treatment, AEs experienced during 1st-line treatment with 4-6 cycles of bevacizumab plus a platinum doublet-containing chemotherapy regimen followed by a minimum of 2 cycles of bevacizumab (monotherapy) maintenance prior to PD1 (ongoing AEs all grades; resolved AEs grade ≥ 3), results of histological/cytological analyses, tumor location and staging, and genetic information (e.g. EGFR mutation status) if available.
- Standard 12-lead ECG.
- Complete physical examination and measurement of vital signs (including height, weight and blood pressure).
- ECOG PS (see Section 5.3.3).
- Blood sampling for serum pregnancy test (see Section 5.4.1) and assessment of laboratory parameters (see Section 5.4).
- Urinalysis (see Section 5.4).
- Tumor assessment (see Section 5.3.1).
- AEs: After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in). All other AEs should be documented with the medical history.
- QoL (assessed using the European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30/QLQ-LC13 questionnaire, described in Section 5.3.5 and included in Appendix 2.
- RCR sampling (optional; see Section 5.4.2).

Patients who fulfill all the inclusion and none of the exclusion criteria will be accepted into the trial.

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

A screen failure log must be maintained by the investigator.

5.2 PROCEDURES FOR RANDOMIZATION OF ELIGIBLE PATIENTS

Patients where written informed consent has been obtained and who satisfy all eligibility criteria, can be randomized into the trial. As eligibility will not be confirmed centrally, it is the responsibility of the investigator to ensure that each patient meets all eligibility criteria. In the event there are any questions or doubts about a patient's eligibility, the investigator site should contact its designated Roche representative (i.e. study monitor) before enrolling the patient.

The investigator site will be provided with a unique trial patient identification number via the eCRF, at the time of individual patient enrolment. The patient numbers will be allocated sequentially in the order in which the patients are enrolled.

The investigator or designee will use the IWRS/IVRS to randomize the patient into the trial and will enter enrollment data into the eCRF.

A Patient Enrollment and Identification Code List must be maintained by the investigator.

Eligible patients will be randomly assigned to treatment groups. Randomization will be performed through a central stratified block randomization process using the following stratification factors:

- Type of planned 2nd-line treatment (erlotinib vs. docetaxel vs. pemetrexed)
- Number of cycles of bevacizumab maintenance treatment prior to PD1 (≤ 6 vs. > 6)
- Smoking status (never vs. former vs. current)

5.3 CLINICAL ASSESSMENTS AND PROCEDURES

All assessments will be scheduled as indicated in Table 1. Additional assessments may be performed as clinically indicated.

All material used for the baseline assessment and assessment of follow-up of patients, or for the investigation of AEs, may be duplicated and made available to the Sponsor for review on request, e.g., for further assessment of the safety profile of the trial treatment, quality assurance purposes etc.

5.3.1 Tumor assessments and response criteria

Tumor assessments will be performed at baseline and at each tumor assessment time point (Table 1), and will consist at minimum of CT scans (high resolution if possible) of the chest and upper abdomen, using i.v. contrasts (for imaging of liver and adrenal glands). All tumor assessments must be performed using the same imagery technique throughout the trial. The same investigator should make measurements for all assessments for each patient.

Patients known to have bone metastasis at baseline, or displaying clinical or biological signs (e.g., serum ALP > 1.5 ULN) of bone metastasis, should undergo an isotope bone scan (this procedure is not mandatory if an ^{18}FDG PET scan has already been performed). CT/MRI scan of the brain is not mandatory, but should be performed as soon as possible if there is a clinical suspicion of CNS metastasis.

Response evaluation criteria in solid tumors (RECIST v1.1) will be used to evaluate tumor response. A summary of the RECIST v1.1 criteria is provided in Appendix 1.

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

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

Scheduling of tumor assessments

Baseline total tumor burden (at PD1) must be assessed within a maximum of 28 days before first dose of trial drug treatment, with the aim being to assess tumor burden as close to the first dose as possible.

Post-baseline assessments are to be performed at the following time points (see Table 1):

- At completion of every 2nd cycle during 2nd-line treatment
- At the Response Assessment visit, at least 4 weeks after any tumor response
- At completion of every 3rd cycle during 3rd-line and subsequent lines of treatment.
- Progression Assessment visit, once PD2/PD3/PD4 is/are observed.
- For patients in the follow-up phase: Every 12 weeks prior to PD3.
- Final visit for patients on treatment or prior to PD3.

The PD1 assessment will serve as baseline for determining PD2. The PD2 assessment will serve as baseline for determining PD3. The PD3 assessment will serve as baseline for determining PD4, etc.

If there is suspicion of new PD based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed to confirm new PD by repeat scan.

If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation (with the exception of the Response Assessment visit), the patient may continue treatment until the next scheduled assessment, unless signs of clinical progression are present. If there is suspicion of new PD based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Additionally, the PD may be so evident in some cases that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression will be based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy with appropriate imaging.

Complete and partial responses must be confirmed no less than 4 weeks after the criteria for response are first met. The confirmatory radiology should be performed within 4 to 6 weeks. In case of SD, follow-up measurements must have met the SD criteria at least once after trial entry at a minimum interval of 6 weeks.

5.3.2 Clinical efficacy assessments

Duration of survival, PFS and time to PD2/3/4 will be assessed until trial end. Duration of survival is defined as the time period from randomization to death. Time to PD2/3/4 is defined as the time period from randomization to PD2/3/4.

5.3.3 Performance status

PS will be measured using the ECOG Performance Status Scale (see Appendix 3).

It is recommended, where possible, that a patient's PS will be assessed by the same person throughout the trial.

PS will be assessed as described in (Table 1).

5.3.4 Clinical safety assessments

All assessments will be scheduled as indicated in the Schedule of Assessments (Table 1). Additional assessments may be performed as clinically indicated.

Clinical assessments will include prior medical history, prior cancer therapies and PS; these may include a CT / MRI scan of the brain (only in patients with symptoms/signs suggestive of CNS involvement or other unexplained neurological symptoms).

A symptom-directed physical examination will be performed at each visit or as indicated, including measurement of vital signs (height [at baseline only], weight and blood pressure)

The NCI-CTCAE version 4.0 will be used to evaluate the clinical safety of the treatment in this trial (see Appendix 4). Patients will be assessed for all AEs, SAEs, and AEs of special interest at each clinical visit and as necessary throughout the trial. All AEs will be recorded into the eCRF pages. Further details on definition, collection and reporting of AEs are provided in Section 5.5 and Section 7.

Concomitant therapies, as outlined in Section 4.4 need to be recorded in the eCRF at each trial visit.

Safety assessments in line with local standard of care or those that are symptom-directed should be undertaken at the discretion of the treating physician.

A standard 12-lead ECG will be performed within 28 days prior to Day 1, Cycle 1 and repeated during the trial as clinically indicated.

Within 30 days after the last bevacizumab / SOC treatment administration, patients will undergo a safety follow-up assessment, including general physical examination, measurement of vital signs, ECOG PS, laboratory assessments and AE follow-up.

LVEF will only be assessed in the event of symptomatic cardiac failure and should be repeated every 3 weeks until resolution or stabilization of the event. The same assessment method should be used throughout the trial.

5.3.5 Quality of life assessments

QoL will be assessed using the EORTC QLQ-C30/QLQ-LC13. The QLC-C30 has been shown to be a reliable and valid measure of the QoL of cancer patients in multicultural clinical research settings. The QLQ-LC13 module has also been shown to be a clinically valid and useful tool for assessing disease- and treatment-specific symptoms in lung cancer patients participating in clinical trials, when combined with the QLQ-C30.

The QLQ-C30 is a self-administered, cancer-specific questionnaire with multidimensional scales; it consists of five functional domains (physical, role, emotional, cognitive, and social); three symptom domains (fatigue, nausea/vomiting, and pain); six single items (dyspnea, sleep, appetite, constipation, diarrhea, and financial impact) and a global QoL domain. The QLQ-C30 comprises 30 questions.

In addition, the QLQ-LC13 module addresses specific issues in lung cancer patients that may not be addressed adequately by the core questionnaire QLQ-C30. The module comprises 13 questions incorporated into one multi-item scale designed to evaluate dyspnea and a series of single items assessing different types of pain, as well as cough, hemoptysis, dysphagia, sore mouth, alopecia, and peripheral neuropathy.

For each domain and item, a linear transformation is applied to standardize the raw score to a range from 0 to 100, with 100 representing best possible function/QoL, and highest burden of symptoms for symptom domains and single items.

The QLQ-C30/QLQ-LC13 questionnaire will be used in all countries for which a validated translation is available in a language in which the patient is fluent. Each patient should complete a questionnaire once at each of the following time points:

- Baseline (within 7 days prior to Cycle 1 Day 1)
- At every cycle until the completion of 3rd-line treatment (for patients stopping treatment prematurely every 12 weeks prior to PD 3)

- At every 2nd bevacizumab cycle until cessation of bevacizumab; and 30 days after last dose
- Final visit (for patients on treatment or prior to PD3).

Patients should complete the questionnaires at the beginning of each visit, before any extensive contact and consultation with the clinician/trial investigator, as the consultation may bias the patient's perceptions about his or her health-related QoL.

For questionnaires completed at the beginning of a cycle, the patient's answers should be based on his or her QoL over the entire period elapsed since the previous questionnaire.

The site staff should ensure appropriate identifiers (i.e. date of completion and patient study number) are recorded each time a questionnaire is filled in.

The QLQ-C30/QLQ-LC13 will be scored as recommended by the developers. For the QLQ-C30/QLQ-LC13 tool, higher scores indicate better QoL.

5.4 LABORATORY ASSESSMENTS

The time points for laboratory tests are defined in the Schedule of Assessments (Table 1).

Additional tests may be performed at the discretion of the investigator.

In order to determine a patient's eligibility for the trial, hematology, coagulation tests, blood chemistry, urinalysis and serum pregnancy test (female patients) have to be performed within 2-28 days (see Table 1) of patient inclusion and recorded in the Screening section of the eCRF.

Local laboratories will be used for all laboratory tests, with abnormal test results for the laboratory test recorded in the AE section of the eCRF Section 7.1.3. Sample handling procedures will comply with Good Laboratory Practices.

The total volume of blood loss for laboratory assessments will be approximately 15 mL per cycle.

5.4.1 Safety laboratory assessments

Regular safety assessments should be taken in accordance with local standard of care, and include:

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count
- Coagulation tests (INR and aPTT or equivalent)
- Biochemistry: serum chemistry (including total protein [or albumin only], ALP, AST/SGOT, ALT/SGPT, total bilirubin, creatinine, estimated CrCl)
- Urinalysis by dipstick. In case proteinuria ≥ 2+ is detected by the dipstick method, a 24-hour urine collection is needed to confirm renal function is within acceptable limits (< 1 g per day).

- Pregnancy test: WOCP will have a serum pregnancy test no more than 7 days prior to the first trial treatment or no more than 14 days (with a confirmatory urine pregnancy test within 7 days prior to the first trial treatment). This test will be repeated if there is any likelihood that a female patient may be pregnant (not required for women who have undergone, and have documentation of a hysterectomy).

5.4.2 Roche Clinical Repository (RCR) of biomarker samples and assessments

Specimens for **dynamic (non-inherited) biomarker** discovery and validation will be collected from consenting patients.

These specimens will be used for research purposes to identify dynamic biomarkers that are predictive of response to bevacizumab treatment (in terms of dose, safety and tolerability) and will help to better understand the pathogenesis, course and outcome of NSCLC and related diseases. To these ends analysis may include determination of markers such as VEGF, VEGFR-1, VEGFR-2, neuropilins, angiopoetins, PlGF and bFGF. Specimens for dynamic biomarker discovery will be single coded like any other clinical sample (labeled and tracked using the patient's trial identification number.

Specimens for **genetic biomarker (inherited**) discovery and validation will also be collected from consenting patients.

The pharmacogenetic information gathered through the analysis of specimens in the RCR is hoped to improve patient outcome by predicting which patients are more likely to respond to specific drug therapies, predicting which patients are susceptible to developing adverse side effects and/or predicting which patients are likely to progress to more severe disease states. Such genetic samples collected for analysis of heritable DNA variations will be double coded: a new independent code will be added to the first code to increase confidentiality and data protection.

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

Plasma assays

Blood (two approximately 6 mL samples in EDTA) for plasma isolation will be obtained at baseline, after every 4 cycles while patient is receiving trial drug, and then at end of treatment, as shown in Table 1 (Schedule of assessments). Blood sampling for plasma isolation will stop for patients receiving study treatment beyond 4th-line. These samples will be used for biomarker assays which may include but are not limited to VEGF, sVEGFR1/R2, PlGF, ICAM, bFGF and other candidate NSCLC biomarkers.

Blood sample for genetic analysis

Whole blood (approximately 6 mL in K3 EDTA) for DNA isolation will be collected at baseline shown in Table 1 (Schedule of assessments). It is highly recommended that this be done prior to randomization to ensure that samples

are collected from patients who withdraw. If, however, the RCR genetic blood sample is not collected during the scheduled visit, it may be collected at any time (after randomization) during the conduct of the clinical trial. The sample may be processed using techniques such as kinetic PCR and DNA sequencing.

Archival Tumor Tissue Sampling

Tumor tissue collection is optional in this trial and written informed consent will be obtained. The rationale for the tissue collection is described in Section 3.1.1.

Twenty slides of formalin fixed tumor tissue embedded in paraffin blocks will be collected for all consenting patients. Slides should be freshly cut from formalin fixed tumor tissue embedded in paraffin blocks (or parts of tumor tissue blocks for disposition at Roche) of primary tumor (or metastatic sites, if the primary tumor is not available), with minimal necrosis. If tissue from rebiopsies is available, it will be collected and analysed in a similar way. The study does not require any tissue removal but uses archival tissue obtained during routine care.

The following assessments may be performed on the tumor tissue but are not limited to:

- Expression of NRP 1
- Expression of VEGF A, VEGF-R1, VEGF-R2
- Expression of CD31
- Expression of cMet

The material will be used for IHC analysis and DNA/RNA extraction. Additional methodologies may be applied for corroboration, including RT-PCR, in situ hybridization, and gene expression profiling. The collected tumor tissue and blood samples may be used to develop and validate diagnostic assays and might allow the generation of statistically meaningful biomarker data.

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

All RCR specimens will be destroyed no later than 15 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period. The specimens in the RCR will be made available for future biomarker research towards further understanding of treatment with bevacizumab, of NSCLC, related diseases and AEs, and for the development of potential associated diagnostic assays. The implementation and use of the RCR specimens is governed by the RCR policy to ensure the appropriate use of the RCR specimens.

For all samples, dates of consent and data on specimen collection should be recorded on the associated RCR page of the eCRF.

RCR sampling will be continued as outlined in Table 1.

5.5 POST-TRIAL PROVISION OF CARE

All patients in Arm A will receive bevacizumab as long as required per protocol for the duration of the trial.

At the end of the trial (see Section 3.1.3), patients still receiving treatment will continue to receive bevacizumab (provided by the Sponsor) until next PD (patients on 2nd-line treatment can receive bevacizumab until PD3) is diagnosed or unacceptable toxicity, or patient withdrawal, or until an absolute contraindication to repeated treatment arises (or a decision is made to stop treatment).

Consenting patients will be rolled over into a separate protocol designed to allow treatment continuation until PD for patients from various bevacizumab Roche studies. In this protocol, safety information, study drug administration, disease progression and survival data will be collected.

All other patients will receive post-trial treatment for NSCLC at the investigator's discretion.

At the safety follow-up visit, the investigator should instruct each patient to report to the investigator any subsequent adverse events.

After study closure, the Sponsor should be notified if the investigator becomes aware of any death, serious adverse event, or other non-serious AEs of special interest occurring at any time after a patient has discontinued study participation regardless of the relationship to the study drug.

The investigator is not required to actively monitor patients after the study has ended. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the investigator should report the event directly to local Roche affiliate.

6. DOSING AND SCHEDULING

For "Pharmaceutical Particulars of Bevacizumab" see Appendix 5.

In the uncommon case of a patient having a CR, further treatment is at the discretion of the investigator. The patient will remain in the study for further follow-up. All details will be clarified on a case by case basis with the Roche Medical Monitor or his/her designee.

6.1 DOSE AND SCHEDULE OF BEVACIZUMAB

The dose of 7.5 mg/kg or 15 mg/kg of bevacizumab will be administered intravenously every 21 days ± 3 days. The approved (per label) dose (7.5 or 15 mg/kg i.v.) and Q3W schedule of bevacizumab used during 1st-line and maintenance treatment should be the same dose and schedule administered to

each patient during the study. This same bevacizumab dose and Q3W schedule must be continued throughout all lines of treatment for the duration of the trial in any given patient.

At each cycle, bevacizumab must be administered before SOC treatment at the same clinic visit, as erlotinib is taken orally the patient is allowed to follow his normal schedule. Rationale for dose selection is given in Section 3.1.2. The first dose of bevacizumab will be administered in a similar fashion to 1st-line treatment. If this is not known, the investigator should follow the standard instructions for first time administration (see Appendix 5)

6.1.1 Dose modifications and delays

Bevacizumab dose will not be reduced for reasons other than a > 10% change in weight from baseline. If i.v. SOC treatment is delayed, bevacizumab administration must also be delayed. If erlotinib is delayed bevacizumab treatment can continue unless the reason for the delay of erlotinib would also result in holding bevacizumab. Missed doses will not be administered subsequently. Treatment can not be omitted for more than 42 days. Restarting bevacizumab treatment after missing more than 42 days must be discussed with the Roche Medical Monitor or his/her designee.

Bevacizumab dose adjustments for body weight changes are not required unless the patient's body weight changes by at least 10% from baseline.

In cases of toxicity, please refer to the current version of the bevacizumab Investigator's Brochure for guidance.

6.1.1.1 General Remarks on Grade 3 or 4 Bevacizumab-Related Events

First occurrence:

- hold bevacizumab until toxicity has resolved to baseline or at least improved to CTCAE v4.0 grade ≤ 1 (with exception of the special cases outlined below and in Section 7.3.1).

Second occurrence upon reintroduction:

- If grade 3 toxicity recurs upon reintroduction of bevacizumab, the investigator should consider the individual benefit versus the risk of continuing the bevacizumab therapy. If the event occurs again upon a second reintroduction of bevacizumab, bevacizumab treatment should be permanently discontinued.
- If a second episode of grade 4 toxicity occurs, permanently discontinue treatment.

If the first occurrence was during the 1st-line treatment, this should be counted. Please see also Section 5.1 for guidance of reporting those AEs.

As described below, bevacizumab treatment may be either temporarily or permanently suspended in the case of hypertension, proteinuria, thrombosis/embolism, hemorrhage, CHF or wound healing complications in addition to any other serious bevacizumab-related toxicity (grade 3 or 4).

Bevacizumab should be temporarily withheld in the event of febrile grade 4 neutropenia and/or grade 4 thrombocytopenia (regardless of the relationship to treatment), since these conditions are predisposing factors for an increased bleeding tendency. For appropriate management for grade 3 or 4 bevacizumab-related events is described below

In addition, bevacizumab treatment should be permanently discontinued in patients experiencing any of the following events:

- Grade 4 hypertension (hypertensive crisis).
- RPLS.
- Nephrotic syndrome.
- Grade 3/4 hemorrhagic/bleeding events, including
  - any grade CNS bleeding.
  - grade ≥ 2 hemoptysis.
- Thromboembolism
  - any grade of arterial thromboembolism.
  - grade 4 venous thromboembolism.
- Any grade of gastrointestinal perforation.
- Fistulae
  - any grade of tracheo-esophageal fistula.
  - grade 4 non-gastrointestinal fistula.
- Grade 3/4 CHF.

6.1.1.2 Hypertension

Patients must be closely monitored on trial for the development or worsening of hypertension. Blood pressure measurements should occur after the patient has been in a resting position for ≥ 5 minutes. If the initial BP reading is ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic pressures, the result should be verified with a repeat measurement. If hypertension occurs, bevacizumab treatment should be managed as described below

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.

6.1.1.3 Reversible Posterior Leucoencephalopathy Syndrome (RPLS)

There have been rare reports of patients treated with bevacizumab that develop signs and symptoms consistent with RPLS, a rare neurological disorder, which can present with following signs and symptoms among others: seizures, headache, confusion, visual disturbance or cortical blindness, with or without associated hypertension. Brain imaging confirms the diagnosis of RPLS.

Bevacizumab treatment should be discontinued in patients who develop signs/symptoms consistent with RPLS and the specific symptoms should be appropriately treated, including control of hypertension.

6.1.1.4 Proteinuria

Proteinuria will be assessed within 48 hours before each bevacizumab treatment by dipstick method unless assessed by 24-hour urine collection. An algorithm for the appropriate management graded according to NCI CTC-AE 4.0 following a positive dipstick result with corresponding bevacizumab treatment management guidance is provided below (Table 3).

Table 3 Bevacizumab treatment management for proteinuria

NCI CTCAE v4.0 grading	Urinalysis	Treatment action
Grade 1	1+ proteinuria urinary protein < 1.0 g/24 hrs	No bevacizumab dose modifications
Grade 2	2+ proteinuria urinary protein 1.0-3.4 g/24 hrs	Suspend bevacizumab for urine protein level ≥ 2 g/24 hrs and resume when proteinuria is < 2 g/24 hours For 2+ dipstick: may administer bevacizumab; obtain 24-hour urine prior to next bevacizumab dose For 3+ dipstick: obtain 24-hour urine prior to bevacizumab administration
Grade 3	Urinary protein > 3.5 g/24 hrs	Suspend bevacizumab. Resume when proteinuria is < 2 g/24 hrs, as determined by 24-hrs urine collection < 2.0 g.
Nephrotic syndrome		Discontinue bevacizumab.

6.1.1.5 Hemorrhage

Bevacizumab should be permanently discontinued for:

- Any grade of CNS bleeding: permanently discontinue bevacizumab. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in case of intracranial bleeding of any grade.
- Grade ≥ 2 hemoptysis.
- Grade 3 or 4 bleeding of any other kind.

If hemorrhagic complications occur in patients on full dose anticoagulation treatment, permanently discontinue bevacizumab treatment and follow guidelines of the institution. Standard procedures such as antagonisation with protamine or vitamin K, infusion of vitamin K dependent factors or insertion of a vena cava

filter should be considered dependent on the severity of the bleeding and thrombotic events and the organ affected.

Dose modifications for the selected SOC treatment are outlined in Section 6.5.

6.1.1.6 Thrombosis/embolism

Arterial thromboembolism: If a patient experiences any grade of arterial thromboembolism during the trial treatment period, bevacizumab should be discontinued permanently.

Venous thromboembolism: Patients experiencing a grade 4 thrombosis must be discontinued from the trial.

If a patient experiences a grade 3 venous thromboembolism, bevacizumab must be withheld for 21 days. Bevacizumab may be resumed during the period of therapeutic-dose anticoagulant treatment.

6.1.1.7 Dose interruption due to infusion-associated reactions

For administration guidelines, see Appendix 5.

- In case of an infusion-related reaction a 90-minute infusion or up to 24 hours later, the next infusion must be administered over at least 120 minutes. If the 120 minute infusion is well tolerated, the next infusion and all subsequent infusions may be delivered over 120 minutes.
- If any infusion-related reaction occurs during a 60 minute infusion or up to 24 hours later, the next infusion must be administered over 90 minutes. If the 90 minute infusion is well tolerated, the next infusion and all subsequent infusions may be delivered over 90 minutes.
- If an infusion-related reaction occurs during a 30-minute infusion or up to 24 hours later, all subsequent infusions may be delivered over 60 minutes or longer.

6.1.1.8 Surgical procedures and wound healing complications

Bevacizumab treatment should be withheld for an interval of at least four weeks (28 days) before conducting elective surgery. In the case of unplanned surgical procedures, bevacizumab should be stopped as soon as the indication for surgery is identified. Emergency surgery should be performed as appropriate without delay after a careful risk benefit assessment.

Bevacizumab treatment should be restarted ≥ 28 days and ≤ 42 days following major surgery. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. If the wound is not fully healed within 42 days, bevacizumab treatment should be discontinued.

Continuation of trial treatment in patients who have had bevacizumab treatment delayed for more than 42 days due to surgical procedures or wound healing must also be discussed with the Roche medical monitor or his/her designee.

6.2 FORMULATION, PACKAGING, LABELLING, PREPARATION AND ADMINISTRATION OF BEVACIZUMAB

For detail regarding the formulation, packaging, labeling, preparation and administration of bevacizumab, see Appendix 5.

6.3 DOSE AND SCHEDULE OF SECOND-LINE STANDARD OF CARE TREATMENT

Use of SOC treatment will be in accordance with the relevant local guidelines and SmPC. Management (i.e. handling, storage, administration and disposal) will be in accordance with GCP and local guidelines.

- Use normally available commercial stock in keeping with the usual practice of the institution.
- There are no special accountability arrangements for erlotinib, docetaxel or pemetrexed
- Below is a summary of the guidelines which should be used as guidance in this protocol

6.3.1 Dose and schedule of erlotinib

The dose of erlotinib is 150 mg daily taken on an empty stomach at least one hour before or two hours after the ingestion of food.

6.3.2 Dose and schedule of docetaxel

Docetaxel should generally not be given to patients with bilirubin > ULN, or to patients with SGOT/AST and/or SGPT/ALT > 1.5 x ULN concomitant with ALP > 2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with ALP are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase > 1.5 x ULN also have a higher rate of febrile neutropenia grade 4.

- The dose of docetaxel is 60 or 75 mg/m^2 i.v. in 500 mL normal saline or 5% dextrose (according to local label and the standard practice of the institution) via a rate-controlling device over 1 hour on Day 1 every 21 days (± 3 days).
- Reconstitute and administer via a non-PVC giving set and connectors incorporating a filter ≤ 0.22 µm.
- Monitor closely for allergic reactions and cardiac arrhythmias as per local institution guidelines.

Premedication for Docetaxel

All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

6.3.3 Dose and schedule of pemetrexed

The dose of pemetrexed is 500 mg/m^2 i.v. over 10 minutes on Day 1 every 21 days (± 3 days).

Premedication for pemetrexed

All patients treated with pemetrexed must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related toxicity. To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The premedication doses administered are in compliance with the SmPC.

Folic Acid

Patients will obtain folic acid in one of the following forms, with preference in order from Option 1 to Option 3:

1. 350 to 600 µg folic acid.
2. A multivitamin containing folic acid in the range of 350 to 600 µg (acceptable only if Option 1 is not available).
3. A dose of folic acid between 600 and 1000 µg (acceptable only if neither Option 1 nor Option 2 is available).

For purposes of this trial, all patients should take oral folic acid daily, beginning approximately 1 to 2 weeks prior to the first infusion of pemetrexed, and continuing daily until 21 days after discontinuation of pemetrexed.

Vitamin B_{12}

Vitamin B_{12} will be prescribed by the investigator and administered as a 1000 µg intramuscular injection. A vitamin B_{12} injection must be administered approximately 1 to 2 weeks prior to the first pemetrexed infusion, and should be repeated approximately every 9 weeks. Equivalent sub cutaneous administration is permitted.

Dexamethasone

Dexamethasone 4 mg (or an equivalent corticosteroid and dose) will be given orally twice per day, the day before, the day of, and the day after each dose of pemetrexed.

6.4 DOSE AND SCHEDULE OF THIRD AND SUBSEQUENT LINES OF STANDARD OF CARE TREATMENT

Following PD2 or intolerance to 2nd-line SOC treatment, a new, locally approved SOC agent may be selected for subsequent 3rd-line treatment. The choice and administration schedule of agent will be according to local standards of care. Bevacizumab must continue to be given in 21-day cycles (± 3 days). An approved SOC agent not initially administered as 2nd-line treatment may be subsequently selected e.g. if a patient received erlotinib as 2nd-line treatment, then either docetaxel, pemetrexed, or another approved agent can be used in 3rd-

line or subsequent line treatment. Similarly, following PD3, a new, approved SOC agent may be selected for subsequent treatment according to local standards of care.

An investigational treatment is only allowed following PD3. No anti-angiogenesis treatment, other than bevacizumab, is allowed in Arm A, and no anti-angiogenesis treatment is allowed in Arm B. Should the investigator decide to treat the patient with an investigational drug in 4th or later line, bevacizumab treatment will be stopped.

6.5 DOSE MODIFICATIONS AND DELAYS OF STANDARD OF CARE TREATMENT

Dose modifications and toxicity management of SOC treatment will be in accordance with the relevant local guidelines and SmPC. Below is a summary of the guidelines which should be used as guidance in this protocol.

6.5.1 Erlotinib

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

Diarrhea and skin rash are the major side effects associated with erlotinib. Other known side effects of erlotinib include dry skin, fatigue, pruritus, nausea, vomiting, anorexia, abdominal pain, gastrointestinal perforation, dry mouth, dry eye, and headache. Dose reduction to 100 mg daily can be made according to the system exhibiting the greatest degree of toxicity. All toxicities will be graded according to the NCI CTC-AE version 4.0.

Upon the onset of an AE deemed by the investigator to be related to erlotinib, treatment will be interrupted until AE resolution and then restarted at 100 mg daily. Once a patient has a dose reduction for toxicity, the dose will not be re-escalated except in the case of erlotinib-related rash.

The following guidelines in Table 4 outline dose adjustments according to the most common toxic effects. In the event of a rash, dose can be re-escalated when rash is ≤ grade 2. Should a patient experience more than one toxic effect, the dose should be reduced.

If symptoms of the same degree reoccur after re-initiating the treatment at reduced dose patients should cease erlotinib.

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

Missed doses:

Doses should be taken at the same time each day. If the patient vomits after ingesting the tablets, the dose will be replaced only if the tablets can actually be seen and counted. A missed dose normally taken in the morning can be taken

any time during the same day. Patients will be asked to report any missed doses to trial site personnel.

Table 4 Guidelines for management of erlotinib-related toxic effects

Toxicity	Grade	Guideline for management	Dose modification of erlotinib*
Keratitis	2	Interrupt the treatment. Ophthalmologic assessment.	Hold until recovery, and then restart at reduced dose. Continue regular ophthalmological assessments while on treatment.
	≥ 3	Discontinue treatment and seek ophthalmological advice	
Diarrhea	1	No intervention	None
	2	Loperamide (4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea-free for 12 hours)	None**
	3		Hold until recovery to ≤ grade 1, and then restart at reduced dose.
	4	Discontinue treatment	
Rash	1	No intervention	None
	2	Any of the following: minocycline[a], topical tetracycline or clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)	None**
	3		Hold until recovery to ≤ grade 2, and then restart the dose.
	4	Discontinue treatment	
Other toxicity	≥ 2 prolonged clinically significant toxicity	Treatment as appropriate	Hold until recovery to ≤ grade 1, and then restart at reduced dose.

* If no recovery after 14 days of holding drug, patients should cease erlotinib

** If dose has been previously held for grade 2 rash or diarrhea, and grade 2 symptoms recur, or if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1 and then reduce the dose.

a. Recommended dose: 200 mg p.o. b.i.d. (loading dose), followed by 100 mg p.o. b.i.d. for 7-10 days.

6.5.2 Docetaxel

Dose adjustments should be determined based on clinical assessment on Day 1 of each treatment cycle.

Docetaxel will not be re-escalated once reduced. If a dose reduction for docetaxel beyond –2 is required or if docetaxel is held for more than six weeks (from the date of last docetaxel treatment), docetaxel and prednisone should be discontinued.

For the initial dose-limiting toxicity (DLT), reduce the dose of docetaxel from 75 mg/m^2 to 65 mg/m^2, select an alternate agent. For the 2nd DLT, reduce the dose to 55 mg/m^2. For any subsequent DLT, docetaxel must be ceased permanently.

In countries, in which 60 mg/m^2 is the labeled dose, dose reduction should follow the local label.

6.5.2.1 Hematologic toxicity

Dose adjustments for hematologic toxicity with docetaxel are shown in Table 5.

Table 5 Dose adjustments for hematologic toxicity with docetaxel

Day 1 of each cycle			
ANC/mm^3	and/or	Platelets/mm^3	Docetaxel
≥ 1,500		≥ 100,000	100%
< 1,500		< 100,000	Hold*

* Hold docetaxel and bevacizumab. Repeat counts weekly and resume all treatment when ANC ≥ 1,500/mm^3 and platelets ≥ 100,000/mm^3. If treatment is held for more than one week, resume with docetaxel at one lower dose level.

Following episodes of grade 3 or 4 neutropenia (ANC < 1000/mm^3), consideration should be given to the use of G-CSF for subsequent cycles.

For febrile neutropenia during any cycle, defined as ANC < 500/mm^3 and T ≥ 38.2°C, docetaxel should be decreased one dose level for all subsequent cycles.

No bevacizumab dose modifications will be made for hematologic toxicity.

6.5.2.2 Hepatic toxicity

Dose adjustments for hepatic toxicity with docetaxel are shown in Table 6.

Table 6 Dose adjustments for hepatic toxicity with docetaxel

Day 1 of each cycle			
Bilirubin	and/or	AST	Docetaxel
≤ 1.5 ULN		> 1.5 to 5 x ULN	Decrease by one dose level
> 1.5 ULN		> 5 x ULN	Hold*

* Hold docetaxel until bilirubin ≤ 1.5 x ULN or AST ≤ 1.5 – 5 x ULN. Resume with docetaxel at one lower dose level.

6.5.2.3 Neurotoxicity

For grade 3 or 4 neurotoxicity, hold both docetaxel and bevacizumab until the toxicity resolves to grade 2 or less and then resume treatment with docetaxel at one lower dose level. If the disability persists or worsens despite dose reduction, hold both docetaxel and bevacizumab until toxicity clears to grade 2 or less then

resume with docetaxel at one more lower dose level. If treatment is held for more than six weeks (from the date of last docetaxel treatment) or if disability persists after 2 dose reductions, discontinue docetaxel and prednisone.

6.5.2.4 Gastrointestinal toxicity

For ≥ grade 3 oral ulceration, dysphagia, diarrhea, nausea or vomiting, hold both docetaxel/prednisone and bevacizumab. Resume with docetaxel at one lower dose level once symptoms resolve to grade 1 or less.

6.5.2.5 Gastrointestinal perforation and wound breakdown

For any grade gastro-intestinal perforation, gastro-intestinal leak, intra-abdominal fistula, and wound dehiscence requiring medical or surgical intervention, discontinue bevacizumab and docetaxel/prednisone.

6.5.2.6 Fluid retention

If symptomatic, treat the patient early with diuretics of the physician's choice. If the patient is not responsive to diuretics, continue docetaxel and bevacizumab treatment without prednisone. If fluid retention remains refractory, discontinue docetaxel and prednisone.

6.5.2.7 Cutaneous toxicity

Hold both docetaxel and bevacizumab for grade 3 or 4 toxicity until the toxicity resolves to grade 2 or less and then resume with docetaxel at one lower dose level. If toxicity recurs, discontinue docetaxel and prednisone.

6.5.2.8 Hypersensitivity

In the event of any grade 3 or 4 hypersensitivity reactions, discontinue all current treatment. For grade 1 hypersensitivity, slow the rate of docetaxel infusion until resolution of symptoms, then complete infusion at the initial planned rate. For grade 2 hypersensitivity, stop the infusion; give diphenhydramine 50 mg i.v. with dexamethasone 10 mg i.v. plus an H2 blocker, all at the physician’s discretion. Resume docetaxel infusion after recovery. Pretreat with diphenhydramine and H2 blocker for future cycles.

6.5.3 Pemetrexed

Treatment with pemetrexed should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after 2 dose reductions (except alopecia, which does not warrant treatment discontinuation) if a Grade 3 or 4 neurotoxicity is observed.

6.5.3.1 Hematologic toxicity

Treatment can be delayed for up to 21 days until the Day 1 ANC is $\geq 1.5 \times 10^9$/L and the platelet count is $> 100 \times 10^9$/L. If the counts have not recovered in 21 days, pemetrexed will be discontinued. Continuation of treatment after a delay of more than 21 days must be discussed with the Roche Medical Monitor or his/her designee.

Pemetrexed may be dose-reduced for hematologic toxicity as described in Table 7.

Table 7 Dose Modification for Pemetrexed Hematologic Toxicities

Toxicity*	Dose Reduction
ANC < 500/mm^3 and platelets ≥ 50,000 /mm^3	75% of previous dose
Platelets < 50,000/mm^3, regardless of ANC	75% of previous dose
Platelets < 50,000/mm^3 with ≥ grade 2 bleeding, regardless of ANC.	50% of previous dose
ANC < 1000/mm^3 plus fever of ≥ 38.5°C	50% of previous dose

* Nadir of last cycle

6.5.3.2 Non-hematologic toxicity

If a patient develops non-hematologic toxicities ≥ grade 3 (excluding alopecia, which does not warrant treatment discontinuation, and neurotoxicity), pemetrexed should be withheld until resolution to less than the patient's pre-therapy value. Treatment should be resumed according to the guidelines in Table 8.

Table 8 Dose Modification Table for Pemetrexed Non-hematologic Toxicities (Excluding Neurotoxicity)

NCI CTC-AE	Dose Reduction
Any grade 3 or 4 toxicities except mucositis and alopecia	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of grade) or grade 3 or 4 diarrhea.	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose

NCI CTC-AE = National Cancer Institute Common Terminology Criteria for Adverse Events

Creatinine Clearance (CrCl) must be 45 mL/min prior to the start of any cycle. If a patient's CrCl value has not returned to 45 mL/min within 42 days of last trial drug administration, pemetrexed must be ceased.

6.5.3.3 Neurotoxicity

Patients should discontinue treatment if grade 3 or 4 neurotoxicity is observed.

6.6 BLINDING AND UNBLINDING

Not applicable; this trial is open-label.

6.7 ACCOUNTABILITY OF IMP AND ASSESSMENT OF COMPLIANCE

6.7.1 Accountability of IMP

A preprinted Drug Dispensing Log will be provided by the Sponsor.

The investigator is responsible for the control of drug under investigation. Adequate records for the receipts (e.g. Drug Receipt Record) and disposition (e.g. Drug Dispensing Log) of the trial drug must be maintained. Accountability and patient compliance will be assessed by maintaining adequate drug storage, drug dispensing, drug inventory, and drug destruction records.

Accurate records must be kept for each trial drug vial provided by the Sponsor. These records must contain the following information:

- documentation of drug shipments received from the Sponsor (date received, quantity and batch identity)
- documentation of continuous drug storage within 2-8^{o} C
- disposition of unused trial drug not administered to a patient

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

- the identification of the patient to whom the trial drug was dispensed
- the date(s), quantity and batch identity of the trial drug administered *to* the patient

This inventory must be available for inspection by the Monitor at every visit. All supplies, including partially used or empty containers and copies of the dispensing and inventory logs, must be returned to the Monitor before the end of the trial, unless alternate destruction has been authorized by the Sponsor, or required by local or institutional regulations.

Any temperature excursions outside of 2-8°C must be quarantined from the usable stock (still within 2-8°C), event should be recorded on the temperature excursion log, and sent to Sponsor for review. Sponsor will inform site if excursion was within limits and can be returned to usable stock.

6.7.2 Assessment of compliance

Patient compliance will be assessed by maintaining adequate trial drug dispensing records. The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator and the Sponsor.

6.8 DESTRUCTION OF BEVACIZUMAB

Local or institutional regulations may require immediate destruction of used trial drug. In these cases, it may be acceptable for investigational site staff to destroy dispensed trial drug before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled

against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the Sponsor at trial start up before destruction.

Written documentation of destruction must contain the following:

- Identity (batch numbers and dispensed patient numbers) of trial drug(s) destroyed
- Quantity per type (100 mg and 400 mg vials) of trial drug(s) destroyed
- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the Sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)
- Name and signature of responsible person who discarded the trial drug in a hazardous container for destruction.

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 ADVERSE EVENTS AND LABORATORY ABNORMALITIES

7.1.1 Clinical adverse events

This trial will comply with all local regulatory requirements. According to the ICH, an AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions (exceptions see Section 7.1.1.5) that worsen during the trial are to be reported as AEs.

7.1.1.1 Intensity

Intensity of all AEs will be graded according to the NCI CTCAE v 4.0 on a five-point scale (Grade 1 to 5) and reported in detail on the eCRF.

Table 9 Grading of adverse events not listed on the Common Terminology Criteria for Adverse Events (CTCAE) v4.0

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

7.1.1.2 Drug – adverse event relationship

The causality relationship of trial drug to the AE will be assessed by the investigator as either:

Yes or No

If there is a reasonable suspected causal relationship to the trial drug, i.e. there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as Yes.

The following criteria should be considered in order to assess the relationship as **Yes**:

- Reasonable temporal association with drug administration
- It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of treatment administered to the patient.
- Known response pattern to suspected drug
- Disappears or decreases on cessation

- Reappears on rechallenge

The following criteria should be considered in order to assess the relationship as **No**:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of treatment administered to the patient.
- It does not follow a known pattern of response to the suspected drug.
- It does not reappear or worsen when the drug is readministered.

7.1.1.3 Serious adverse events (immediately reportable to The Sponsor)

A SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. These must be reported to The Sponsor immediately (no more than 24 hours after learning of the event) through the eSAE page in the eCRF. It is any AE that at any point fulfils at least one of the following criteria:

- is fatal (i.e., the adverse event actually causes or leads to death)
- is Life-Threatening (i.e. the adverse event, in the view of the investigator, places the patient at immediate risk of death).

  Note: this does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- requires or prolongs in-patient hospitalization
- results in persistent or significant disability/incapacity (i.e. the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- is medically significant in the investigator's judgement (e.g. may jeopardize the patient or may require medical/surgical intervention to prevent one or other of the outcomes listed above).

The term sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably.

The trial will comply with all local regulatory requirements and adhere to the full requirements of the **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2** (see Appendix 6 and trial-specific manuals for details).

After informed consent, but prior to initiation of trial drugs, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive

procedures such as biopsies, medication washout, or no treatment run-in). SAEs related to trial-specific procedures need to be reported starting right after the patient has signed the Informed Consent Form even if the SAE commenced before the patient received the first dose of trial drug.

7.1.1.4 Adverse Events of Special Interest

Some AEs have been reported as associated with the use of bevacizumab treatment. Further details are provided in the Investigator Brochure. Considering the extensive clinical use acquired with bevacizumab across its indications in over 1,000,000 patients, only the most clinically relevant will be considered as AEs of special interest for this trial, and will undergo specific reporting.

Additional information on the following AEs of special interest (at any grade) will therefore be captured during this trial:

- Hypertension
- RPLS
- Proteinuria
- Hemorrhage, with a focus on hemoptysis and CNS bleeding
- Arterial and venous thromboembolic events
- Wound healing complications
- Gastro-intestinal perforation
- Fistulae
- CHF

7.1.1.5 Progression of underlying malignancy

Progression of underlying malignancy is not reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST v1.1 criteria, or other criteria as determined by protocol (see Appendix 1). Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a SAE. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under trial.

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

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

7.1.2 Treatment and follow-up of adverse events

After the last bevacizumab infusion, continue to follow up AEs as follows:

Related AEs: Follow until one of the following occurs:

- Resolved or improved to baseline
- Relationship is reassessed as unrelated
- Death
- Investigator confirms that no further improvement can be expected (stabilization)
- Clinical or safety data will no longer be collected, or final database closure

Related SAEs are to be reported indefinitely.

Unrelated severe or life-threatening AEs: Follow until one of the following occurs:

- Resolved or improved to baseline
- Severity improved to Grade 2
- Death
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected, or final database closure

Unrelated Grade 1 or Grade 2 AEs: Follow for 30 days after cessation of bevacizumab.

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

Adverse events of special interest: Should be followed-up for 6 months.

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

At the safety follow-up visit, the investigator should instruct each patient to report to the investigator any subsequent adverse events.

After study closure:

After study closure, the Sponsor should be notified if the investigator becomes aware of any death, serious adverse event, or other non-serious AEs of special interest occurring at any time after a patient has discontinued study participation regardless of the relationship to the study drug.

The investigator is not required to actively monitor patients after the study has ended. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

7.1.3 Laboratory test abnormalities

Local laboratories will be used for all laboratory tests, with test results for the laboratory test described in Section 5.4.1 recorded in the laboratory results section of the eCRF.

Laboratory test value abnormalities should not be recorded in the AE section of the eCRF as AEs, unless they are considered clinically significant, as defined below.

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g. dose modification, interruption or permanent discontinuation)
- Results in a medical intervention (e.g. potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinical significant in the investigator's judgement.

  Note: for oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 ×ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 7.1.6 for details on recording persistent adverse events).

7.1.4 Follow-up of abnormal laboratory test values

In the event of a medically significant, unexplained abnormal laboratory test value, the test should be repeated and followed until it has returned to the normal

range, baseline value and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

7.1.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 7.1.6 for details on recording persistent adverse events).

7.1.6 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 7.2.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

7.1.7 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All

adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 7.2.2).

7.1.8 Adverse Events in Individuals Not Enrolled in the Study

If an adverse event inadvertently occurs in an individual not enrolled in the study (e.g., during administration of study drug), the Adverse Event Form provided to investigators should be completed and submitted to Roche or its designee, either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

7.2 HANDLING OF SAFETY PARAMETERS

7.2.1 Reporting of adverse events

All AEs, SAEs, and AEs of special interest, regardless of the relationship to trial drug, will be recorded in the eCRF.

All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to trial drug, action taken with the trial drug, outcome, and whether the AE is classified as serious.

All AEs (either related to trial specific procedures or otherwise) experienced after the patient has signed the Informed Consent form but before they have received trial treatment, should be recorded as medical history. Only SAEs caused by a protocol mandated intervention that are experienced after the patient has signed the Informed Consent form but before they have received trial treatment should be reported as SAEs.

All AEs experienced after the patient has started trial treatment and up to 30 days after the last dose of trial treatment must be recorded on the AE form of the eCRF (see also Section 7.1.2.). SAEs considered related to trial drug are to be reported indefinitely.

Progression of underlying malignancy see Section 7.1.1.5 **is not to be reported as an (S)AE**

Signs and symptoms of the underlying NSCLC should only be reported if:

- Newly emergent (i.e. not present at baseline) and the association with the underlying malignancy and old/new metastatic lesions is unclear and/or
- The investigator attributed deterioration of the NSCLC signs and symptoms directly to the trial drug

Should there be any uncertainty regarding the attribution of the NSCLC to the AE, it should be reported as an AE or a SAE accordingly.

Laboratory test results will be recorded on the laboratory results eForms of the eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.

A medical condition (e.g. elevated laboratory value) already existent before first treatment should not be reported as an AE unless the condition worsens.

If the AE increases in severity, the investigator must re-assess the event to determine if an AE must be reported (determine attribution).

If the AE resolves and then recurs, the investigator should re-assess the event in case the second AE occurred more than 3 days after the end date of the preceding AE. In case of a shorter interval, the AE should not be reported separately.

At the safety follow-up visit, the investigator should instruct each patient to report to the investigator any subsequent adverse events.

After study closure, the Sponsor should be notified if the investigator becomes aware of any non-serious AEs of special interest occurring at any time after a patient has discontinued study participation regardless of the relationship to the study drug. The investigator is not required to actively monitor patients after the study has ended.

The investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the investigator should report the event directly to local Roche affiliate.

The following adverse events of special interest require reporting to the Sponsor immediately (no more than 24 hours after learning of the event).

- Hypertension ≥ grade 3
- Proteinuria ≥ grade 3
- GI perforation, GI abscesses and GI fistulae (any grade)
- Wound healing complications ≥ grade 3
- Haemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 haemoptysis)
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ grade 3
- RPLS (any grade)
- CHF ≥ grade 3
- Non-GI fistula or abscess ≥ grade 2

7.2.2 Reporting of Serious Adverse Events (immediately reportable)

Any clinical adverse event or abnormal laboratory test value that is *serious* and which occurs during the course of the study (as defined in Section 7.1.1.3 above; see Appendix 7), regardless of the treatment arm, occurring from the enrollment visit (start of study screening procedures), including long term follow-up (LTFU)

must be reported to the Sponsor no more than 24 hours after learning of the event (expedited reporting). The investigator must complete the *SAE Reporting Form [gcp_for000031]* and forward it to the SAE Responsible. All SAEs occurring from the enrollment period must be reported, (start of study screening procedures).

Events that occur prior to study drug initiation: After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in). The Serious Adverse Event / Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

After first study medication, all SAEs must be reported.

Related Serious Adverse Events ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to investigators at each site and associated IRB/IEC when the following conditions occur:

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

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

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

Unrelated Serious Adverse Events must be collected and reported during the study and for up to 30 days after the last dose of study medication.

After study closure, the Sponsor should be notified if the investigator becomes aware of any death or serious adverse event occurring at any time after a patient has discontinued study participation regardless of the relationship to the study drug.

The investigator is not required to actively monitor patients after the study has ended. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the investigator should report the event directly to local Roche affiliate.

This study adheres to the definition and reporting requirements of **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2**. Complete information can be found in Appendix 6.

7.2.3 Pregnancy

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Angiogenesis has been shown to be critically important to fetal development. The inhibition of angiogenesis following administration of bevacizumab could result in an adverse outcome of pregnancy. Therefore, bevacizumab should not be used during pregnancy. Female patients with childbearing potential or amenorrhoeic for < 24 months must have a negative serum pregnancy test (see Section 5.4.1) prior to randomization into the trial and agree to use an effective method of contraception during the trial, and for a period of 6 months following the last administration of bevacizumab.

A female patient must be instructed to stop taking the trial drug and immediately inform the investigator if he/she becomes pregnant during the trial. The investigator should report all pregnancies within 24 hours to the Sponsor. The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 90 days after the completion of bevacizumab must also be reported to the investigator.

Male patients should not father a baby whilst on trial treatment. Fertile male patients participating in the trial must practice an acceptable method of effective birth control while on treatment and for 6 months following the last administration of bevacizumab. Pregnancy occurring in the partner of a male patient participating in the trial should be reported to the investigator and the Sponsor. The partner should be counselled, the risks of continuing the pregnancy discussed, as well as the possible effects on the fetus. Monitoring of the partner should continue until conclusion of the pregnancy.

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

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

7.3 WARNINGS AND PRECAUTIONS

7.3.1 Warnings and precautions relating to bevacizumab

No evidence available at the time of the approval of this trial protocol indicated that special warnings or precautions were appropriate with regards to bevacizumab treatment, other than those noted in the current version of the Investigator's Brochure.

7.3.1.1 Hypertension

An increased incidence of hypertension was observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab treatment. Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. Monitoring of blood pressure is recommended during bevacizumab treatment.

Patients with uncontrolled hypertension should be excluded from participation in this trial (see Section 4.3). Details on dose delays in the event of bevacizumab-related events of hypertension are provided in Section 6.1.1.

7.3.1.2 Reversible Posterior Leucoencephalopathy Syndrome (RPLS)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder, which can present with following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients developing RPLS, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab treatment in patients previously experiencing RPLS is not known.

7.3.1.3 Proteinuria

In clinical studies, 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 bevacizumab. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during bevacizumab treatment.

Details on dose delays in the event of bevacizumab-related proteinuria are provided in Section 6.1.1.4. In the event of grade 4 proteinuria, bevacizumab treatment should be permanently discontinued.

7.3.1.4 Hemorrhage

An increased incidence of bleeding events was observed in patients treated with bevacizumab as compared to control treatment arms. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage.

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 hemorrhage in such patients has not been prospectively evaluated in randomized clinical studies. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in case of intracranial bleeding of any grade.

Pulmonary hemorrhage/hemoptysis has been observed across indications. Serious and in some cases fatal pulmonary hemorrhage/hemoptysis has been observed in patients with advanced or recurrent NSCLC treated with bevacizumab.

Patients with a history of grade ≥2 hemoptysis, or with history or evidence of inherited bleeding diathesis or coagulopathy with the risk of bleeding, should be excluded from participation in this trial (see Section 4.3).

Bevacizumab should be permanently discontinued in patients who experience grade 3 or 4 of any other bleeding during bevacizumab treatment.

7.3.1.5 Thrombosis/Embolism

In clinical studies, the incidence of arterial thromboembolism events including CVAs, transient ischemic attack, and myocardial infarction was higher in patients receiving bevacizumab in combination with chemotherapy, compared to those who received chemotherapy alone. Bevacizumab should be permanently discontinued in patients who develop arterial thromboembolic events.

Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under bevacizumab treatment. Details on dose delays in the event of bevacizumab-related venous thromboembolic events are provided in Section 6.1.1.5.

7.3.1.6 Gastrointestinal Perforation

Bevacizumab has been associated with serious cases of gastrointestinal perforation or fistulae. Gastrointestinal perforations have been reported in clinical studies with an incidence of < 1% in patients with mBC or non-squamous NSCLC, and up to 2% in mCRC patients. Fatal outcome was reported in approximately one-third of serious cases of gastrointestinal perforations, which represents between 0.2%-1% of all bevacizumab treated patients.

Patients with a history of gastrointestinal perforation should be excluded from participation in this trial (see Section 4.3). Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation.

7.3.1.7 Fistulae

Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the gastrointestinal tract are common in patients with mCRC, but uncommon or rare in other indications. Fistulae that involve areas of the body other than the gastrointestinal tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly in patients receiving bevacizumab in clinical studies and post-marketing reports.

Patients with a history of abdominal fistula should be excluded from participation in this trial (see Section 4.3). Bevacizumab should be permanently discontinued in patients with tracheoesophageal fistulae or any grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of bevacizumab should be considered.

7.3.1.8 Wound Healing

As bevacizumab may adversely impact wound healing, patients who had major surgery within the last 28 days, or minor surgery within 24 hours prior to initiation of bevacizumab treatment, and patients with a non-healing wound, should be excluded from participation in this trial (see Section 4.3).

In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. Bevacizumab treatment should be withheld for elective surgery and elective surgery should be scheduled 4 or more weeks after the last bevacizumab dose given the long half-life.

7.3.2 Warnings and precautions relating to erlotinib

For full details regarding warnings and precaution relating to erlotinib treatment, refer to the current version of the local product label.

7.3.2.1 Interstitial lung disease (ILD)-like events

Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly in patients receiving erlotinib for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In pivotal trial BR 21, in NSCLC, the incidence of serious ILD-like events was 0.8% in each of the placebo and erlotinib arms. In the pancreatic cancer trial in combination with gemcitabine, the incidence of ILD-like events was 2.5% in the erlotinib plus gemcitabine group versus 0.4% in the placebo plus gemcitabine treated group. The overall incidence in patients treated with erlotinib from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Some examples of reported diagnoses in patients suspected of having ILD-like events include pneumonitis, radiation pneumonitis, hypersensitivity

pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, lung infiltration and alveolitis. These ILD-like events started from a few days to several months after initiating erlotinib treatment. Most of the cases were associated with confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever, erlotinib treatment should be interrupted pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued and appropriate treatment initiated as necessary.

7.3.2.2 Diarrhea, dehydration, electrolyte imbalance and renal failure

Diarrhea has occurred in patients on erlotinib, and moderate or severe diarrhea should be treated with loperamide. In some cases, dose reduction may be necessary. In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, erlotinib treatment should be interrupted and appropriate measures should be taken to treat the dehydration. There have been rare reports of hypokalaemia and renal failure (including fatalities). Some reports of renal failure were secondary to severe dehydration due to diarrhea, vomiting and/or anorexia while others were confounded by concomitant chemotherapy. In more severe or persistent cases of diarrhea, or cases leading to dehydration, particularly in groups of patients with aggravating risk factors (concomitant medications, symptoms or diseases or other predisposing conditions including advanced age), erlotinib treatment should be interrupted and appropriate measures should be taken to intensively rehydrate the patients intravenously. In addition, renal function and serum electrolytes including potassium should be monitored in patients at risk of dehydration.

7.3.2.3 Hepatitis and hepatic failure

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

7.3.2.4 Gastro-intestinal perforation

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

7.3.2.5 Bullous and exfoliative skin disorders

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

7.3.2.6 Ocular disorders

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

7.3.2.7 Toxicity due to drug interactions

Erlotinib has a potential for clinically significant drug-drug interactions (see Appendix 9).

7.3.3 Warnings and precautions relating to docetaxel

7.3.3.1 Hypersensitivity

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and aggressive treatment. Patients with a history of severe hypersensitivity reactions should not be rechallenged with docetaxel. Hypersensitivity reactions may occur within a few minutes following initiation of a docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of treatment is not required. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of docetaxel.

7.3.3.2 Hematologic toxicity

Neutropenia (< 2000 neutrophils/mm^3) occurs in virtually all patients given 60-100 mg/m^2 of docetaxel and grade 4 neutropenia (< 500 cells/mm^3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^2. Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. Docetaxel should not be administered to patients with neutrophils < 1500 cells/mm^3.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m^2 but was very uncommon in patients given 60 mg/m^2. Hematologic responses, febrile reactions and infections, and rates or septic death for different regimens are dose related.

In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving docetaxel. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3. A 25% reduction in the dose of docetaxel is recommended during subsequent cycles following severe neutropenia (< 500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a docetaxel cycle.

7.3.3.3 Acute myeloid leukemia

Treatment-related acute myeloid leukemia (AML) or myelodysplasia has occurred in patients given anthracyclines and/or cyclophosphamide, including use in adjuvant treatment for breast cancer.

7.3.3.4 Cutaneous toxicity

Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended. The discontinuation rate due to skin toxicity was 1.6% for mBC patients. Among 92 breast cancer patients premedicated with corticosteroids for 3 days, there was no case of severe skin toxicity reported and no patient discontinued docetaxel due to skin toxicity.

7.3.3.5 Fluid retention

Severe fluid retention has been reported following docetaxel treatment. Patients should be premedicated with oral corticosteroids prior to each docetaxel administration to reduce the incidence and severity of fluid retention. Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg. Among 92 breast cancer patients premedicated with corticosteroids for 3 days, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m^2. Fluid retention led to treatment discontinuation in 9.8% (9/92) of patients: 4 patients discontinued with severe fluid retention; the remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m^2. Fluid retention was completely, but sometimes slowly, reversible with a median of 16 weeks from the last infusion of docetaxel to resolution (range: 0 to 42+ weeks). Patients developing peripheral edema may be treated with standard measures, e.g., salt restriction, oral diuretic(s).

7.3.3.6 Neurotoxicity

Severe neurosensory symptoms (paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of mBC patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms

persist, treatment should be discontinued. Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

7.3.4 Warnings and precautions relating to pemetrexed

For full details regarding warnings and precaution relating to pemetrexed treatment, refer to the current version of the local product label.

7.3.4.1 Myelosuppression

Pemetrexed can suppress bone marrow function as manifested by neutropenia, thrombocytopenia and anemia (or pancytopenia).

Myelosuppression is usually the DLT. Patients should be monitored for myelosuppression during treatment and pemetrexed should not be given to patients until ANC returns to ≥ 1500 cells/mm^3 and platelet count returns to ≥ 100,000 cells/mm^3. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-hematological toxicity seen from the previous cycle.

Less toxicity and reduction in grade 3/4 hematological and non-hematological toxicities such as neutropenia, febrile neutropenia and infection with grade 3/4 neutropenia were reported when pre-treatment with folic acid and vitamin B_{12} was administered. Therefore all patients treated with pemetrexed must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related toxicity (see Section 6.3.2).

7.3.4.2 Skin Reactions

Skin reactions, such as rash, desquamation, alopecia and pruritus, have been reported in pemetrexed-treated patients not pre-treated with a corticosteroid. Pre-therapy with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions. A corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice per day, the day before, the day of, and the day after each dose of pemetrexed.

7.3.4.3 Renal Insufficiency

An insufficient number of patients has been studied with CrCl < 45 mL/min. Therefore, the use of pemetrexed in patients with CrCl < 45 mL/min is not recommended. Patients with **mild to moderate renal insufficiency** (CrCl from 45 to 79 mL/min) should avoid taking NSAIDs such as ibuprofen, and aspirin (> 1.3 g daily) for 2 days before, on the day of, and 2 days following pemetrexed administration. All patients eligible for pemetrexed treatment should avoid taking NSAIDs with long elimination half-lives for at least 5 days prior to, on the day, and at least 2 days following pemetrexed administration.

Serious **renal events**, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes.

The effect of third-space fluid, such as pleural effusion or ascites, on pemetrexed is unknown. In patients with clinically significant third-space fluid, consideration should be given to draining the effusion prior to pemetrexed administration.

Due to the gastrointestinal toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving treatment.

7.3.4.4 Cardiovascular Events

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors.

7.3.4.5 Immunosuppression

An immunosuppressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines (except yellow fever which is contraindicated) is not recommended.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 PRIMARY AND SECONDARY TRIAL VARIABLES

8.1.1 Primary variable

Overall survival (OS): This is defined as the time from the date of randomization at PD1 to the date of death, regardless of the cause of death. Patients with an unknown survival status at study end will be censored when they were last known to be alive.

8.1.2 Secondary efficacy variables

- The rate of 6-, 12-, and 18-month OS as measured from randomization at progression PD1.
- PFS and TTP from randomization at PD1, to PD2 (PFS2, TTP2), and to PD3
- Response rates, disease control rates, and duration of response at PD2 and PD3.

Progression-free survival: PFS2 is defined as the time between randomization at PD1 and the date of PD2 or death, whichever occurs first. PFS3 is defined as the time between PD2 and the date of PD3 or death, whichever occurs first.

Patients who have neither progressed nor died at the time of trial completion or who are lost to follow-up are censored at the date of the last tumor assessment or last follow up for PD. Patients for whom no post-baseline tumor assessments are available are censored at day of randomization.

Time to progression: TTP2 is defined as the interval between the day of randomization at PD1 and PD2. **TTP3** is defined as the interval between the day of PD2 and PD3. Patients who are withdrawn from the trial without documented progression and for whom there exists eCRF evidence that evaluations have been made, will be censored at the date of the last tumor assessment when the patient was known to be progression free. Patients without post-baseline tumor assessments but known to be alive will be censored at the time of randomization.

Response rates: Objective response in an individual patient is defined as CR or PR, and will be assessed according to the RECIST v.1.1 criteria (Appendix 1), with baseline tumor assessment as the reference. The best objective response in an individual patient according to the RECIST v.1.1 criteria is the best response recorded from the start of the treatment until PD/recurrence (taking as reference for PD the smallest measurements recorded since the baseline assessment), death or within 56 days of last intake of trial drug (whichever comes first). To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

Disease control rate: Disease control in an individual patient is defined as CR or PR or SD, and will be assessed according to the RECIST v.1.1 criteria (Appendix 1), with baseline tumor assessment as the reference. To be assigned a status of PR or CR or SD, changes in tumor measurements must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

Duration of response in 2nd-line or 3rd-line: Duration of response will be measured from the time that measurement criteria are met for objective response (CR/PR) (whichever status is recorded first) until the first date that PD2 (in 2nd-line) or PD3 (in 3rd-line) or death is documented. This analysis will include patients with objective response being CR or PR only. Patients who neither progressed nor died will be censored at the date of the last tumor assessment.

8.1.3 Exploratory efficacy variables

- To compare the efficacy between Asian and non-Asian patients. “Asian” patients will be defined in the Statistical Analyses Plan (SAP).

8.1.4 Safety

Patients who did not receive at least one dose of any trial drug will be excluded from the analysis of safety.

Tables of AE incidence (preferred term classification) and individual incidence will be produced. All AEs, including SAEs and AEs of special interest will be summarized by treatment arm and severity grade. In addition, AEs leading to

discontinuation of trial treatment will be summarized by treatment arm. For each patient's AEs, the maximum severity recorded will be used in the summaries.

Dose reductions for SOC treatment and reasons for premature withdrawals from all trial drugs will also be described.

Laboratory data will be presented both as summary of the absolute values and as differences from baseline values over time. Reference ranges provided by the Sponsor will be used for the analysis of marked laboratory abnormalities.

Vital signs will be presented in listings as well as in summaries by time windows.

8.1.5 Quality of Life

The objective of the QoL assessment is to detect and compare changes in patient-reported toxicity effects and lung cancer symptoms over the duration of the trial. Clinically important difference thresholds will be used to define the proportion of patients that improve, remain stable, or worsen.

The QoL scores will be described at baseline and for each visit in order to assess changes from baseline. These data will be compared between the 2 treatment arms. If the number of questionnaires collected is sufficient, other exploratory analyses may be performed, including subgroup analysis (e.g., based on age, ECOG PS).

Mean change from randomization at PD1 in domain scores of QLQ-C30/QLQ-LC13[58] at each time point.

The following definitions will be applied:

- A patient will be considered as having a clinically meaningful improvement in his health-related QoL if the change in the score increases by at least 10 points.
- A patient will be considered as having a clinically meaningful degradation of his health-related QoL if the change in the score decreases by at least 10 points.
- A patient will be considered as having no change in health-related QoL if the patient does not fall into either category above.

8.2 STATISTICAL AND ANALYTICAL METHODS

8.2.1 Analysis populations

Intent-to-treat (ITT): The ITT population will consist of all consenting patients randomized to trial treatment. Patients will be assigned to treatment groups based on what they were randomized to receive.

Per-Protocol (PP): The PP population is a subgroup of the ITT population containing all patients who do not have any major protocol violation and received trial therapies (bevacizumab and SOC treatment in Arm A or SOC treatment alone [Arm B]) at least once. Major violations will include, but are not limited to: violation of inclusion/exclusion criteria, administration of non-allowed SOC drug

for patients in Arms A and B, erroneous administration of bevacizumab for patients in Arm B. Details will be provided in the SAP.

The primary efficacy analysis will be based on the ITT population. All efficacy analyses will be repeated using the PP population to confirm the overall trial results.

Safety: The safety population will comprise all patients who received at least one dose of trial drug. Patients will be assigned to treatment groups based on what they actually received.

All safety analyses will be based on the safety population.

8.2.2 Efficacy analysis

8.2.2.1 Primary variable

The primary efficacy analysis for this trial will compare duration of OS beyond progression for bevacizumab plus SOC treatment or SOC treatment alone. OS will be summarized by Kaplan-Meier curves. Median survival estimates as well as associated 90% CIs will be reported for each treatment arm. The difference in OS between the two treatment arms will be tested with a stratified log-rank test. The hazard ratio of overall survival will be estimated using a stratified Cox regression model with the same stratification factors used in the stratified log-rank test. The primary analysis will be performed on the ITT population and PP population.

8.2.2.2 Secondary variables

The duration of PFS (PFS2, PF3) for patients who have not died (or are not known to have died, or are lost to follow-up) at the time of analysis will be censored as of the date the patient was last known to be progression-free. Differences in PFS between treatment arms will be tested with a stratified log-rank test (stratified on the stratification factors used at randomization). Kaplan-Meier curves will be displayed, with median PFS estimates and confidence limits provided.

Response rates and disease control rates will be summarized by treatment arm and the estimated difference in response rates and the associated 90% CIs will be provided. The Cochran-Mantel Haenszel test, stratified by the same factors used at randomization, will be used to compare the overall response rate between the treatment arms. An unadjusted Chi-squared test result will also be provided.

Differences in duration of response will be tested for descriptive purposes with a stratified log-rank test. Kaplan-Meier curves will be displayed, with median duration estimates and confidence limits provided.

All comparisons will be based on the ITT population and repeated for the PP population.

The primary and secondary variables will also be analysed for the subgroup of adenocarcinoma patients. More details will be specified in the Statistical Analysis Plan.

8.2.2.3 Exploratory variables

Exploratory subgroup population (Asian or non-Asian) will be analyzed in the same fashion as the primary and secondary endpoints.

8.2.3 Safety analysis

All safety parameters will be presented based on the safety population, defined as all patients who received at least one dose of trial drug after randomization.

AEs will be presented in frequency tables. Laboratory data will be presented as summary statistics for each sampling time point using both shift and frequency tables. All AEs and abnormal laboratory variables will be assessed using the NCI CTC-AE v.4.0.

Descriptive statistics will be used to summarize ECOG PS.

Vital signs will be presented in listings as well as in summaries by time windows.

Information on trial drug will be summarized by duration, starting dose and cumulative dose using descriptive statistics.

8.2.4 Quality of Life analysis

QoL will be assessed using the core module, EORTC QLQ-C30, and lung cancer specific module, QLQ-LC13.

The QoL scales will be summarized by descriptive summary tables at baseline (randomization at PD1) and over time. Mixed model repeated measures will be used to compare between arms in 2nd-line and between lines of therapies. Missing data will be handled according to the EORTC User's Manual.

The proportion of patients with improvement, degradation, or no change in their health related QoL will be summarized by descriptive summary tables at baseline and over time. The Cochran-Mantel Haenszel test stratified by the same factors used to stratify the randomization will be used to compare the response rates between the treatment arms at the end of treatment. An unadjusted Chi-squared test result will also be provided. To demonstrate time-to-deterioration in health-related QoL, Kaplan-Meier will be used to estimate median time to deterioration and stratified log-rank test will be used to compare the distribution of time-to-deterioration between treatment arms.

8.2.5 Biomarker analysis

The analysis of the biomarkers will be performed in order to evaluate the prognostic value of each analyzed marker. Descriptive analysis will be conducted first.

The association between each biomarker and prognosis will be analyzed by Cox proportion hazards model and logistic regression for time-to-event endpoints and

tumor response endpoints, respectively. The interaction between treatment and each of the biomarkers on prognosis will also be assessed.

Exploratory descriptive and graphical analyses of the time course of plasma biomarkers and tumor size assessments will be produced.

8.2.6 Interim analysis

No formal interim analysis will be conducted.

8.3 SAMPLE SIZE

The sample size calculation for this trial is based on a 45-month recruitment period and minimum follow-up of 12 months.

The NSCLC Phase III 2nd-line trial (BeTa) reported a median OS of 9.2 months for the erlotinib control arm.63 However, in this current study patients will have completed a minimum of 6 cycles of 1st-line bevacizumab-based therapy including a minimum of 2 cycles of maintenance therapy with bevacizumab monotherapy. The current study population is therefore likely to be more similar to the patients included in the retrospective analyses of ARIES as presented in Section 1.1.2.2.

Assuming a median OS beyond progression (PD1) of 10 months (1-year OS rate 43.5%) in the control group, and 10.1 12.8 months (1-year OS rate 52.3%) in the treatment arm (corresponding to a hazard ratio of 0.78), approximately 416 events are required to achieve 80% power for the log-rank test at a twoone-sided significance level of 5%. To allow for a 2% drop-out rate, approximately 500 patients are required (250 per treatment arm). Under the study assumptions, the time to observe 416 events is estimated to be 57 months. The final efficacy analysis will be conducted when either 416 events are observed or after 60 months study duration, whichever occurs first. Data Quality Assurance

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

Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the investigator's records by the trial monitor (source document verification), and the maintenance of a drug–dispensing log by the investigator.

Data for this trial will be recorded via an EDC system using eCRFs. Patient data will be transcribed by the site from the paper source documents onto the eCRF. (In no case is the eCRF to be considered as source data for this trial.)

A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks in the Sponsor database will verify the data and discrepancy reports will be generated accordingly and transferred electronically to the eCRF at the site for resolution by the investigator.

The result of the analysis must not be released with individual identification of the patient until the database is closed.

8.4 ASSIGNMENT OF PREFERRED TERMS AND ORIGINAL TERMINOLOGY

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for adverse events and diseases and the International Non-proprietary Name (INN) Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

9. TRIAL COMMITTEES

9.1 INDEPENDENT STEERING COMMITTEE

A Trial Steering Committee (SC) of expert physicians in the area of NSCLC will be convened for this trial. The SC will meet periodically to discuss the protocol design, the progress of the trial, any relevant issues or trial questions, and eventually the trial results.

The roles and responsibilities and specific policies of the SC will be described in a separate document, the Steering Committee Charter.

9.2 DATA MONITORING COMMITTEE

An IDMC will be established for the MO22097 trial and specific policies on the operation of the IDMC will be documented in a Charter. The IDMC will be responsible for independently evaluating the safety and efficacy of the patients participating in the trial and will be led by a medically qualified Chairperson experienced in the treatment of NSCLC and members will consist of one other physician experienced in the treatment of NSCLC as well as one biostatistician. No member of the IDMC may be from a participating site. The IDMC will meet on a regular basis over the course of the trial and may also meet on an unscheduled basis if any unexpected safety concerns arise. These meetings may occur via videoconference, teleconference, or in person. The IDMC Chair or a designated member (with the assistance of the biostatistician) will prepare minutes within one week following each IDMC meeting.

The roles and responsibilities and specific policies of the IDMC will be described in a separate document, the IDMC charter.

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PART II: ETHICS AND GENERAL TRIAL ADMINISTRATION

11. ETHICAL ASPECTS

11.1 LOCAL REGULATIONS / DECLARATION OF HELSINKI

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

In other countries where "Guideline for Good Clinical Practice" exist Roche and the investigators will strictly ensure adherence to the stated provisions.

11.2 INFORMED CONSENT

Main Informed Consent:

It is the responsibility of the investigator, or a person designated by the investigator ((i.e. a sub-investigator and only if acceptable by local regulations and Sponsor), to obtain written, informed consent from each patient participating in this trial, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the trial. For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and her/his legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the patients are completely free to refuse to enter the trial or to withdraw from it at any time, for any reason and with no effect to their normal care or treatment. The eCRFs for this trial contain a section for documenting patient informed consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give their written consent to continue in the trial.

RCR Informed Consent:

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

The eCRF for the associated clinical trial contains a page for documenting patient informed consent to the RCR, and this must be completed appropriately.

Patient's willingness (or unwillingness) to participate in optional RCR sampling should not affect in any way his/her eligibility to participate in main protocol.

11.3 DEATH OR LOSS OF COMPETENCE OF PARTICIPANT WHO HAS DONATED A SPECIMEN(S) THAT IS STORED IN THE RCR

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

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

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

11.4 INDEPENDENT ETHICS COMMITTEES / INSTITUTIONAL REVIEW BOARD

Independent Ethics Committees [non-US]: This protocol, the patient informed consent form, and any accompanying material provided to the patient [such as patient information sheets or descriptions of the trial used to obtain informed consent] as well as any advertising or compensation given to the patient, will be submitted by the investigator to an IEC. Approval from the committee must be obtained before starting the trial, and should be documented in a letter to the

investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol or patient informed consent form after receipt of the IEC approval must also be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements.

When no local review board exists, the investigator is expected to submit the protocol and patient informed consent form to a regional committee. If no regional committee exists, Roche will assist the investigator in submitting the protocol to the European Ethics Review Committee.

The European Clinical Trials Directive will be followed where applicable.

Sampling for the RCR is contingent on review and approval for the exploratory biomarker assessments and written informed consent form by an appropriate regulatory body (depending on the country where the trial is performed) and a site's Institutional Review Board (IRB) / Ethics Committee (EC). If a regulatory or site's IRB/ EC does not approve the sampling for the exploratory assessments the section on biomarker sampling will not be applicable.

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

12. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the Sponsor and the investigator (investigator representative[s] in the case of a multicenter trial, i.e. the Steering Committee). Protocol modifications must be prepared by a representative of the Sponsor and initially reviewed and approved by the International Medical Leader and Biostatistician.

All protocol modifications must be submitted to the appropriate IEC or IRB for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change[s] involves only logistical or administrative aspects of the trial (e.g. change in monitor[s], change of telephone number[s]).

13. CONDITIONS FOR TERMINATING THE TRIAL

Both the Sponsor and the investigator reserve the right to terminate the trial at any time. Should this be necessary, both parties will arrange the procedures on an individual trial basis after review and consultation. In terminating the trial, Roche and the investigator will assure that adequate consideration is given to the

protection of the patient's interests. The appropriate IRB/IEC and Regulatory Agencies should be informed accordingly.

14. TRIAL DOCUMENTATION, ECRFS AND RECORD KEEPING

14.1 INVESTIGATOR'S FILES / RETENTION OF DOCUMENTS

The investigator must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. These documents should be classified into two different separate categories [1] Investigator's Trial File, and [2] patient clinical source documents.

The Investigator's Trial File will contain the protocol/amendments, Case Report and Query Forms, IEC/IRB and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. In addition at the end of the trial the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the Investigator's Trial File.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, CT, MRI, pathology and special assessment reports, signed informed consent forms, consultant letters, and patient screening and enrollment logs. The investigator must keep these two categories of documents (including the archival CD) on file for at least 15 years after completion or discontinuation of the trial. After that period of time the documents may be destroyed, subject to local regulations.

Should the investigator wish to assign the trial records to another party or move them to another location, Roche must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and Roche to store these in a sealed container[s] outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

ICH GCP guidelines require that investigators maintain information in the trial patient's records which corroborate data collected on the eCRF(s). Completed eCRF will be maintained by Roche.

14.2 SOURCE DOCUMENTS AND BACKGROUND DATA

The investigator shall supply the Sponsor on request with any required background data from the trial documentation or clinic records. This is particularly

important when eCRFs are incoherent or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete trial records, provided that patient confidentiality is protected.

14.3 AUDITS AND INSPECTIONS

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

14.4 ELECTRONIC CASE REPORT FORMS

Data for this trial will be captured via an EDC system by using an online eCRF. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each patient enrolled, an eCRF must be completed and electronically signed by the Principal investigator from the trial staff. This also applies to records for those patients who fail to complete the trial (even during a pre-enrollment screening period if an eCRF was initiated). If a patient withdraws from the trial, the reason must be noted on the eCRF. If a patient is withdrawn from the trial because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

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

15. MONITORING THE TRIAL

It is understood that the responsible Roche Monitor (or designee) will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial (eCRFs, source notes, and other pertinent data) provided that patient confidentiality is maintained in accord with local requirements.

It will be the Monitor's responsibility to inspect the eCRFs and patients study files/source notes at regular intervals throughout the trial, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The Monitor should have access to laboratory test reports and other patient records needed to verify the entries on the eCRF. The investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

RCR specimens will at all times be tracked in a manner consistent with GCP, by a quality controlled, auditable and validated Laboratory Information Management System, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in the trial protocol and ICF,

respectively. Roche monitors [or designees] and auditors will have direct access to appropriate parts of records relating to patients participating in this trial for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents related to the RCR Research Project.

16. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by an identification code. The investigator should keep a patient enrollment log showing codes, names and addresses. The investigator should maintain documents not for submission to Roche, e.g., patients' written consent forms, in strict confidence.

Given the sensitive nature of genetic data, Roche has implemented a number of additional processes to assure patient confidentiality. All specimens taken for inherited genetic research that will be stored in the RCR (see Section 5.4.2) undergo a second level of "coding". At Roche, the specimen is transferred to a new tube and labeled with a new random number. This is referred to as "Double Coding (De-Identification)". Data generated following the use of these specimens and all clinical data transferred from the clinical trial database and considered relevant, will also be labeled with this same code. The "linking key" between the participant's identification number and this new independent code will be stored in a secure database system. Access to the table linking the participant identification number to the specimen code will be strictly limited and monitored by audit trail. Legitimate operational reasons for accessing the "linking key" will be documented in a standard operating procedure. Access to the "linking key" for any other reason will require written approval from the Governance Committee responsible for the specimen(s).

17. CLINICAL STUDY REPORT (CSR)

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

18. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this trial may be published or presented at scientific meetings. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to Roche prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, Roche will ~~only~~ generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements. Any formal publication of the trial in which input of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche personnel.

Data derived from RCR specimen analysis on individual patients will not be provided to trial investigators, except where explicitly stipulated in a trial protocol (e.g. if the result is an enrollment criterion). Exceptions may be granted (e.g. if biomarker data would be linked to safety issues). The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on trial data publication.

Any inventions and resulting patents, improvements and / or know- how originating from the use of the RCR will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

19. APPENDICES

19.1 APPENDIX 1 NEW RESPONSE EVALUATION CRITERIA IN SOLID TUMORS – VERSION 1.1 – MODIFIED EXCERPT FROM ORIGINAL PUBLICATION WITH ADDITION OF SUPPLEMENTARY EXPLANATIONS [1]

Measurability of tumor at baseline

Definitions

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

Measurable Tumor lesions

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

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray (CXR).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also paragraph below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable Tumor lesions

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

Special considerations regarding lesion measurability

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

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

Target lesions: Specifications by methods of measurements

Measurement of lesions

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

Method of assessment

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

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

Chest X-ray: Chest CT is preferred over CXR, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in

identifying new lesions. However, lesions on CXR may be considered measurable if they are clearly defined and surrounded by aerated lung.

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

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

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

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

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

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

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

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions (even if size is greater than 10 mm by CT scan).

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

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (see also "Special notes on assessment of progression of non-target disease").

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

Response criteria

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

Evaluation of target lesions

- *Complete Response (CR):* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- *Partial Response (PR):* At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- *Progressive Disease (PD):* At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial including baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- *Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Special notes on the assessment of target lesions

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

Target lesions that become *'too small to measure'*: while on trial, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

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

Lesions that split or coalesce on treatment: when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions (and, if applicable, normalization of tumor marker level). All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

Special notes on assessment of progression of non-target disease

When the patient also has measurable disease: **in this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of treatment.** A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for **unequivocal progression** status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: this circumstance arises in some phase III trials when it is not a criterion of trial entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural

effusion from ‘trace’ to ‘large’, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as ‘**sufficient to require a change in treatment**’. If ‘unequivocal progression’ is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

New lesions

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

A lesion identified during the trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD.

If a new lesion is equivocal, for example because of its small size, continued treatment and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

*(*Evaluation of response

Time Point Response (Overall response)

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

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

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

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

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

Table 2 Time Point Response – Non-Target Lesions only

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

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

Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and during trial only two lesions were assessed, but those gave a sum of

80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

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

Table 3 Best Overall Response when Confirmation is required

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

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

Special notes on response assessment

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

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

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

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

Frequency of tumor re-evaluation

Reference

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

19.2 APPENDIX 2
QUALITY OF LIFE: EORTC QLQ-C30/QLQ-LC13

QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no 'right' or 'wrong' answers. The information that you provide will remain strictly confidential.

Study MO22097

Investigator Name: _____ Site Number: _____

Patient Number: Date Completed: (dd, mm, yyyy)
_____ / _____ / _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you have to stay in a bed or a chair for most of the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

DURING THE PAST WEEK:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either you work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4

13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

QLQ-LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

DURING THE PAST WEEK:		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of the body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

19.3 APPENDIX 3 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS ASSESSMENTS

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

[1] Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5:649-655, 1982. Also see: http://www.ecog.org/general/perf_stat.html.

19.4 APPENDIX 4
NATIONAL CANCER INSTITUTE-COMMON TOXICITY CRITERIA FOR ADVERSE EVENTS V4.0

The Common Terminology Criteria for Adverse Events v4.0, updated June 14, 2010, is available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

19.5 APPENDIX 5 PHARMACEUTICAL PARTICULARS, PREPARATION AND ADMINISTRATION OF BEVACIZUMAB

1. List of Excipients

- Trehalose dihydrate
- Sodium phosphate
- Polysorbate 20
- Water for injections

2. Incompatibilities

No incompatibilities between bevacizumab and polyvinyl chloride or polyolefin bags have been observed. A concentration-dependent degradation profile of bevacizumab was observed when diluted with dextrose solutions (5%).

3. Stability

Bevacizumab should not be used after the retest date shown on the pack.

4. Special Remarks

4.1 Special Precautions for Storage

Bevacizumab is supplied as a clear to slightly opalescent, colorless to pale brown, sterile liquid for intravenous (i.v.) infusion in single-use vials which are preservative-free.

Bevacizumab will be supplied in 5 mL glass vials with a 4 mL fill (100 mg, 25 mg/mL) and/or in 20 mL glass vials with a 16 mL fill (400 mg, 25 mg/mL). The formulation contains sodium phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI) in addition to bevacizumab active ingredient.

VIALS ARE FOR SINGLE USE ONLY. Vials used for one patient may not be used for any other patient. Vials should not be used after the re-test date shown on the pack.

The labelling of bevacizumab will be in accordance with all local legal requirements and conducted according to Good Manufacturing Practice.

Store vials in a refrigerator at 2°C-8°C (36°F-46°F). Keep vial in the outer carton due to light sensitivity. **DO NOT FREEZE. DO NOT SHAKE**. Protect from light.

Bevacizumab does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-30°C (36°F-86°F) in 0.9% sodium chloride solution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would

normally not be longer than 24 hours at 2°C to 8°C (36°F-46°F), unless dilution has taken place in controlled and validated aseptic conditions.

4.2 Instructions for Use, Handling and Disposal

Bevacizumab should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab for a dose of 7.5 or 15 mg/kg of body weight and dilute in a total volume of 100 mL of 0.9% sodium chloride injection, United States Pharmacopeia (USP). **Bevacizumab infusions should not be administered or mixed with dextrose or glucose solutions**. In case of administering a total dose exceeding 1000 mg, dilute the calculated dose of bevacizumab with a sufficient amount of 0.9% sodium chloride injection to keep final concentration between 1.4 mg/mL and 16.5 mg/mL. Keep 100 mL as the minimal volume to administer and limit the infusion volume as much as possible. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. **Diluted bevacizumab should be used within 8 hours (USP)**.

5. Administration

Administration will be as a continuous i.v. infusion. Anaphylaxis precautions should be observed during trial drug administration.

The first dose of bevacizumab will be administered over 90 minutes. If the first infusion is well tolerated without infusion-related reaction (e.g. fever and/or chills), the 2nd dose will be administered over 60 minutes. If the 2nd dose is also well tolerated without an infusion reaction, all subsequent doses will be administered over 30 minutes).

- In case of an infusion-related reaction during the first cycle (during the 90-minute infusion or up to 24 hours later), the next infusion must be administered over at least 120 minutes. If the 120 minute infusion is well tolerated, the next infusion and all subsequent infusions may be delivered over 120 minutes.
- If any infusion-related reaction occur during the second cycle (during the 60 minute infusion or up to 24 hours later), the next infusion must be administered over 90 minutes. If the 90-minute infusion is well tolerated, the next infusion and all subsequent infusions may be delivered over 90 minutes.
- If an infusion-related reaction occurs during a 30-minute infusion or up to 24 hours later, all subsequent infusions may be delivered over 60 minutes or longer.

A rate-regulating device should be used for all trial drug infusions. When the trial drug i.v. bag is empty, 50 mL of 0.9% sodium chloride solution, USP, will be added to the i.v. bag or an additional bag will be hung, and the infusion will be continued for a volume equal to that of the tubing to ensure complete delivery of the trial drug. The total infusion time, therefore, should always be either 90, 60,

or 30 minutes. If more saline is infused, the extent of saline infusion does not factor into the trial drug infusion time.

Should extravasation of the trial drug infusion occur, the following steps should be taken:

- Discontinue the infusion. Treat the extravasation according to institutional guidelines for extravasation of a non-caustic agent. If a significant volume of the trial drug infusion remains, restart the infusion at a more proximal site in the same limb or on the other side. Treat the infiltration according to institutional guidelines for infiltration of a non-caustic agent.

In the event of a suspected anaphylactic reaction during trial drug infusion:

- Stop the trial drug infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of trial drug. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer antihistamines, corticosteroids, epinephrine, or other medications as required.
- Continue to observe the patient, document observations and administer further treatment as required.

The above events should be reported as AEs.

19.6 APPENDIX 6 ICH GUIDELINES FOR CLINICAL SAFETY DATA MANAGEMENT, DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING, TOPIC E2

An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- is fatal; [results in death] [NOTE: death is an outcome, not an event]
- is Life-Threatening [NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe].
- required in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

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

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

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

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

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

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

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

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

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

The investigator must notify the Ethics Review Committee/IRB of a SAE in writing as soon as is practical and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor [details to be provided separately].

ROCHE HEADQUARTERS CONTACT for SAEs: Clinical Operations/Clinical Science [details to be provided separately].

19.7 APPENDIX 7 EU CLINICAL DIRECTIVES FOR SARS (SERIOUS ADVERSE REACTIONS) MANAGEMENT. DEFINITIONS AND STANDARD FOR EXPEDITED REPORTING

SUSARs:

Suspected Unexpected Serious Adverse Reactions (SUSARs) are suspected adverse reactions related to Investigational Medicinal Products (IMP) and/or comparator(s) (including the placebos), occurring in clinical trials, and are both unexpected and serious.

SUSARs associated with an IMP that does not hold a marketing authorisation and any other SUSARs associated with the IMP, in any Member State (MS) of the European Economic Area, are subject to expedited reporting to Competent Authorities and ethics committees/IRB of the concerned MS, according to the EU-CTD guidelines, as soon as the Sponsor becomes aware of them. This includes SUSARs which:

- Occur in another trial conducted by the same sponsor either in the European Community or in non-European Community countries
- Are identified by spontaneous reports or a publication
- Are transmitted to the Sponsor by another regulatory authority

Other safety issues requiring expedited reporting:

Safety issues that might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the trial, also qualify for expedited reporting, for instance:

- Single case reports of an expected serious adverse reaction with an unexpected outcome (e.g. a fatal outcome)
- An increase in the rate and occurrence of an expected serious adverse reaction which is judged to be clinically important
- Post-trial SUSARs that occur after the patient has completed a clinical trial and are reported by the investigator to the Sponsor
- New events relating to the conduct of the trial or the development of the IMP likely to affect the safety of the patients, such as:
    - An SAE which could be associated with the trial procedure and which could modify the conduct of the trial
    - A significant hazard to the patient population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
    - A major safety finding from a newly completed animal trial (such as carcinogenicity)

Where the IMP is authorised in a MS and the sponsor is the marketing authorisation holder, the reporting of SUSARs should take into account national requirements intended to manage duplication of reports in the context of Directive 2001/83/EC, Regulation 2309/93/EC and the: “Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module)”.

Expedited reporting is usually not required in the following instances:

- Reactions which are serious but expected
- Non-serious adverse reactions, whether they are expected or not
- Events considered unrelated to IMP

Fatal and life threatening SUSARs: Sponsor (F. Hoffmann-La Roche) will report SUSARs to the competent authorities and the EC as soon as possible and not later than 7 calendar days. This reporting is based on receipt from the investigator site of the minimum criteria for expedited reporting. Additional information should be available as soon as possible and reported within an additional 8 calendar days.

In each case, relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the competent authority and the EC in the concerned Member States within an additional eight calendar days.

All other SUSARs and safety issues (requiring expedited reporting) will be reported to the competent authority and EC in the concerned member states as soon as possible and no later than 15 calendar days after F. Hoffmann-La Roche has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be made available as soon as possible.

The distribution to the EC, of the safety letter and CIOMS-I reporting form (with analysis of similar events where produced), will be performed within 15 calendar days from the Roche received date (in all relevant European Economic Area member states).

In case the EC only communicate via investigators, the investigator will forward the information within 7 calendar days from the Roche received date to their ethics committee.

19.8 APPENDIX 8
NYHA CLASSIFICATION

Class	Description
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or angina pain.
II	Patients with cardiac disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
III	Patients with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Oxford Textbook of Internal Medicine. Vol 2, pp 2228. Oxford University Press. 1997	

19.9 APPENDIX 9
INFORMATION ON POTENTIAL INTERACTIONS WITH ERLOTINIB

Erlotinib is metabolized in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2, and the pulmonary isoform CYP1A1. Potential interactions may occur with drugs which are metabolized by, or are inhibitors or inducers of, these enzymes.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. Inhibition of CYP3A4 metabolism by ketoconazole (200 mg po BID for 5 days) resulted in increased exposure to erlotinib (86% in median erlotinib exposure (AUC)) and a 69% increase in C_{max} when compared to erlotinib alone. When erlotinib was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure (AUC) and maximum concentration (C_{max}) increased by 39% and 17%, respectively. Therefore caution should be used when administering erlotinib with potent CYP3A4 or combined CYP3A4/CYP1A2 inhibitors. In these situations, the dose of erlotinib should be reduced if toxicity is observed.

Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. Induction of CYP3A4 metabolism by rifampicin (600 mg p.o. QD for 7 days) resulted in a 69% decrease in the median erlotinib AUC, following a 150 mg dose of erlotinib as compared to erlotinib alone.

Pre-treatment and co-administration of rifampicin with a single 450 mg dose of erlotinib resulted in a mean erlotinib exposure (AUC) of 57.5% of that after a single 150 mg erlotinib dose in the absence of rifampicin treatment. Alternative treatments lacking potent CYP3A4 inducing activity should be considered when possible. For patients who require concomitant treatment with erlotinib and a potent CYP3A4 inducer such as rifampicin an increase in dose to 300 mg should be considered while their safety is closely monitored, and if well tolerated for more than 2 weeks, further increase to 450 mg could be considered with close safety monitoring. Higher doses have not been studied in this setting.

Pre-treatment or co-administration of erlotinib did not alter the clearance of the prototypical CYP3A4 substrates midazolam and erythromycin. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely. Oral availability of midazolam did appear to decrease by up to 24%, which was however not attributed to effects on CYP3A4 activity.

The solubility of erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its bioavailability. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure (AUC) and C_{max} by 46% and 61%, respectively. There was no change to T_{max} or half-life. Concomitant administration of erlotinib with 300 mg ranitidine, an H_2-receptor antagonist, decreased erlotinib exposure (AUC) and C_{max} by 33% and 54%,

respectively. Therefore, co-administration of drugs reducing gastric acid production with erlotinib should be avoided where possible. Increasing the dose of erlotinib when co-administered with such agents is not likely to compensate for this loss of exposure. However, when erlotinib was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg b.i.d., erlotinib exposure (AUC) and C_{max} decreased only by 15% and 17%, respectively. If patients need to be treated with such drugs, then an H_2-receptor antagonist such as ranitidine should be considered and used in a staggered manner. Erlotinib must be taken at least 2 hours before or 10 hours after the H_2-receptor antagonist dosing.

International Normalized Ratio (INR) elevations and bleeding events, including gastrointestinal bleeding, have been reported in clinical studies, some associated with concomitant warfarin administration. Coumarins (Coumadin™; warfarin) use is an exclusion criteria. If the patient requires anti-coagulation treatment, then the use of low molecular weight heparin instead of coumarins is recommended where clinically possible.

In a phase Ib trial, there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine (Core data sheet, 2009).

The following potent CYP3A4 inhibitors may *increase* erlotinib toxicity:

- Systemic antifungals (e.g. ketoconazole, itraconazole, miconazole).
- Erythromycin, clarithromycin, troleandomycin.
- Selective serotonin reuptake inhibitors (e.g. nefazodone).

The following medications could decrease plasma levels of erlotinib and hence decrease efficacy, but they probably do not represent a safety concern:

- Antiepileptics (e.g. carbamazepine, phenobarbital, phenytoin).
- Rifampin, rifabutin.
- Troglitazone.
- Barbiturates.
- Glucocorticoids.
- Saint John’s wort.