ETOP 10-16 BOOSTER

A randomised phase II trial of osimertinib and bevacizumab versus osimertinib alone as second-line treatment in stage IIIb-IVb NSCLC with confirmed EGFRm and T790M

BOOSTER: Osimertinib and Bevacizumab versus Osimertinib alOne as Second-line Treatment in stage IIIb-IVb NSCLC with confirmed EGFRm and T790M

Sponsor: European Thoracic Oncology Platform (ETOP)

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ETOP c/o IBCSG Coordinating Centre, Effingerstrasse 40, CH- 3008 Bern

Phone: +41 31 511 94 00 Fax: +41 31 511 94 01

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Contacts

Trial Chair	Solange Peters, MD-PhD	Address Tel: Fax: Email:	Département d'Oncologie Centre Hospitalier Universitaire Vaudois 1011 Lausanne, Switzerland +41 79 556 01 92 +41 21 314 07 37 solange.peters@chuv.ch
Trial Chair and ETOP Chairman	Rolf Stahel, MD	Address Tel: Fax: Email:	Clinic of Oncology University Hospital Zuerich Raemistrasse 91 CH-8091 Zürich, Switzerland +41 44 255 22 19 +41 44 255 9780 rolf.stahel@usz.ch
Trial Co-Chair	Ross Soo	Address Tel: Fax: Email:	National University Hospital 1E Lower Kent Ridge Road Singapore +6567724140 +6567775545 ross_soo@nuhs.edu.sg
Trial Co-Chair	Ji-Youn Han	Address Tel: Fax: Email:	National Cancer Center 323 Ilsan-ro, Ilsan-dong-gu Goyang, Korea 82-31-920-1154 82-31-920-2587 jymama@ncc.re.kr
Translational Research Coordinator	Rosita Kammler	Address Tel: Fax: Email:	ETOP Coordinating Office c/o IBCSG Coordinating Centre Effingerstrasse 40 3008 Bern, Switzerland +41 31 511 94 28 +41 31 511 94 01 rosita.kammler@ibcsg.org
Central Laboratory		Address	CHUV - Department of oncology Center for Experimental Therapeutics (CTE) Hôpital Orthopédique HO 05/1552 Av. Pierre-Decker 4 CH-1011 Lausanne, Switzerland
Statistics	Urania Dafni, ScD Zoi Tsourti, PhD	Address Tel: Fax: Email: Email:	Frontier Science Foundation – Hellas 116 Papadiamantopoulou Str. 15773, Zografou, Athens, Greece +302107710902 +302107710903 udafni@frontier-science.gr ztsourti@frontier-science.gr
Project Manager Data Management	Mark Finlayson, PhD Anne-Christine Piguet, PhD	Address Tel: Fax: Email: Tel: Fax: Email:	ETOP Coordinating Office c/o IBCSG Coordinating Centre Effingerstrasse 40 3008 Bern, Switzerland +41 31 511 94 34 +41 31 511 94 01 BOOSTER@etop-eu.org +41 31 511 94 21 +41 31 511 94 01 ETOPDataManagement@etop-eu.org

Drug supply	Barbara Ruepp, PharmD	Address Tel: Fax: Email:	ETOP Drug Supply Office c/o IBCSG Coordinating Centre Effingerstrasse 40 3008 Bern, Switzerland +41 31 511 94 16 +41 31 389 92 29 drugsupply@etop-eu.org
Safety and Regulatory Affairs	Barbara Ruepp, PharmD	Address Tel: Fax: Email:	ETOP Safety and Regulatory Office c/o IBCSG Coordinating Centre Effingerstrasse 40 3008 Bern, Switzerland +41 31 511 94 16 +41 31 389 92 29 regulatoryoffice@etop-eu.org
ETOP Medical Affairs	Manuela Rabaglio, MD	Address Tel. Fax : Email :	ETOP Medical Affairs c/o IBCSG Coordinating Centre Effingerstrasse 40 3008 Bern, Switzerland +41 31 511 94 20 +41 31 511 94 01 medical.affairs@ibcsg.org
ETOP Coordinating Office	Anita Hiltbrunner Heidi Roschitzki, PhD	Address Tel: Fax: Email: Tel: Fax: Email:	c/o IBCSG Coordinating Centre Effingerstrasse 40 3008 Bern, Switzerland +41 31 511 94 42 +41 31 511 94 01 anita.hiltbrunner@etop-eu.org +41 31 511 94 18 +41 31 511 94 01 heidi.roschitzki@etop-eu.org
Remote Data Entry system	Anne-Christine Piguet, PhD Technical assistance		ETOPDataManagement@etop-eu.org richard.king@etop-eu.org

In collaboration with AstraZeneca (supply of osimertinib and trial support) and Roche (supply of bevacizumab).

Protocol Signature Page

ETOP 10-16 BOOSTER

A randomised phase II trial of osimertinib and bevacizumab versus osimertinib alone as second-line treatment in stage IIIb-IVb NSCLC with confirmed EGFRm and T790M

Approved by:

Solange Peters
Trial Chair

_____ _____

Date

Rolf Stahel
Trial Chair and
ETOP Chairman

_____ _____

Date

Urania Dafni
Biostatistician

_____ _____

Date

Anita Hiltbrunner
ETOP Director

_____ _____

Date

Principal Investigator Protocol Signature Page

ETOP 10-16 BOOSTER

A randomised phase II trial of osimertinib and bevacizumab versus osimertinib alone as second-line treatment in stage IIIb-IVb NSCLC with confirmed EGFRm and T790M

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

Name of Principal Investigator: _____

Institution's name and place: _____

_____ _____

Signature Date

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ETOP 10-16 BOOSTER

A randomised phase II trial of osimertinib and bevacizumab versus osimertinib alone as second-line treatment in stage IIIb-IVb NSCLC with confirmed EGFRm and T790M

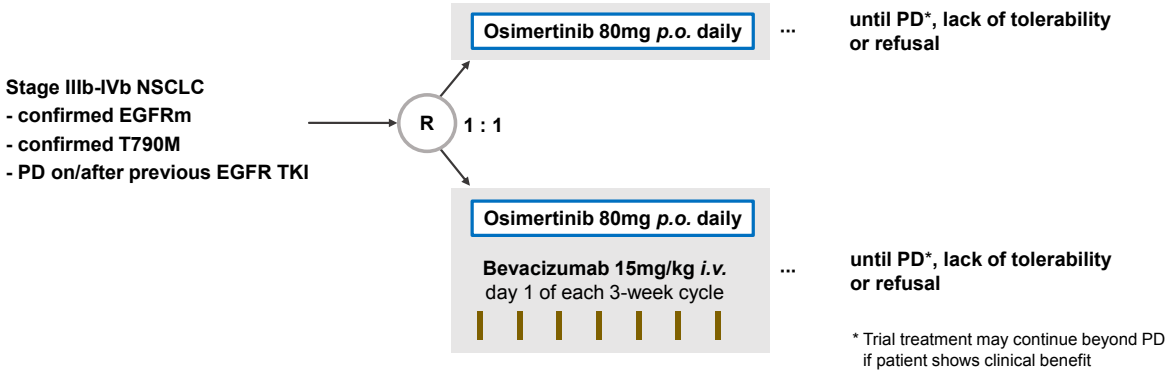
BOOSTER: Osimertinib and Bevacizumab versus Osimertinib alOne as Second-line Treatment in stage IIIb-IVb NSCLC with confirmed EGFRm and T790M

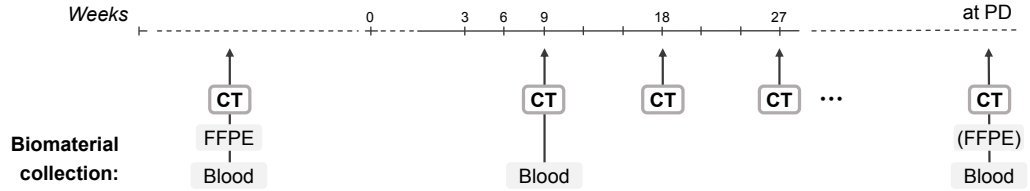
Sponsor: European Thoracic Oncology Platform (ETOP)

Pharma Partner: AstraZeneca

Population: Patients with locally advanced or metastatic (stage IIIb-IVb) EGFRm (exon 19 deletion or exon 21 L858R) NSCLC with T790M resistance mutation at progression on prior EGFR TKI therapy

Design: Open label randomised phase II





Sample size: 154 patients

Randomisation:

Block stratified randomisation balanced by institution.

Stratification factors: Ethnicity (Asian, Non-asian) and material used for T790M testing (tumour vs circulating DNA)

Rationale:

First-generation EGFR tyrosine kinase inhibitors provide significant clinical benefit in patients with advanced EGFR-mutant (EGFRm) non–small cell lung carcinoma (NSCLC).

However, all patients ultimately develop disease progression, driven – as the most prevalent identified biological mechanism – by the acquisition of a second T790M EGFR TKI resistance mutation.

Osimertinib (AZD9291) is a novel oral, potent, and selective third-generation irreversible inhibitor of both EGFRm-sensitizing and T790M resistance mutants. This mono–anilino–pyrimidine compound is structurally distinct from other third-generation EGFR TKIs and offers a pharmacologically differentiated profile from earlier first and second generation EGFR TKIs.

Preclinically, the drug potently inhibits signaling pathways and cellular growth in both EGFRm and EGFRm plus T790M cell line *in vitro*, with lower activity against wild-type EGFR lines.

In the recently published osimertinib phase I trial, a total of 253 patients were treated. Among 31 patients enroled in the dose-escalation cohorts, no dose-limiting toxic effects occurred at the doses evaluated. An additional 222 patients were treated in five expansion cohorts. The most common all-cause adverse events were diarrhoea, rash, nausea, and decreased appetite, however were significantly reduced in occurrence and severity as compared to first/second EGFR TKIs.

The overall objective tumour response rate of osimertinib was 51% (95% CI, 45 - 58). Among 127 patients with centrally confirmed EGFR T790M who could be evaluated for response, the response rate was 61% (95% CI, 52 - 70). In contrast, among 61 patients without centrally detectable EGFR T790M who could be evaluated for response, the response rate was 21% (95% CI, 12 - 34). The median progression-free survival was 9.6 months (95% CI, 8.3 to not yet reached) in patients with EGFR T790M and 2.8 months (95% CI, 2.1 - 4.3) in patients without EGFR T790M. Osimertinib is being evaluated in several prospective clinical trials, notably in frontline treatment, in the adjuvant setting, and in combination with later lines in EGFRm positive advanced disease.

Objectives and endpoints:

Primary objective:

To assess the efficacy of the combination of osimertinib and bevacizumab versus osimertinib alone in terms of progression-free survival (PFS) assessed by RECIST 1.1.

Secondary objectives:

To compare short and long term clinical efficacy outcomes as well as tolerability of the two treatments.

Primary endpoint:

- Progression-free survival (PFS) based on RECIST 1.1 criteria

Secondary endpoints:

- Objective response, based on RECIST 1.1 criteria
- Disease control, defined as complete or partial response, or disease stabilisation, confirmed at subsequent radiological assessment
- Adverse events graded by CTCAE V4.0
- Overall survival

Correlative studies:

- T790M evolution in tissue and plasma/serum (between baseline and relapse)
- Monitoring of mutation burden and specific EGFR mutations (del19, L858R, T790M) in sequential plasma/serum samples
- Analysis of bevacizumab/osimertinib resistance mechanism in relapse biopsy samples (Next Generation Sequencing)

Most important eligibility criteria (see Section 7 for complete list)**:**

Inclusion criteria

- NSCLC, stage IIIb/IIIc (not amenable to radical therapy) or IVa/IVb according to 8th TNM classification, after progression following prior EGFR TKI (erlotinib, gefitinib, dacomitinib or afatinib) therapy as the most recent treatment regimen.
- Pathological diagnosis of predominantly non-squamous NSCLC.
- Maximum of one line of previous platinum based chemotherapy.
- Histological or cytological confirmation of EGFRm (exon19 deletion or exon 21 L858R).
- Locally confirmed T790M mutation determined from biopsy (preferred) or on circulating tumour DNA, documented in tissue, plasma or serum after disease progression on the most recent EGFR TKI regimen.
- Plasma, serum, and tumour (preferred) tissue or cytology (if biopsy was taken and FFPE tumor material is not yet fully depleted) after disease progression on the most recent EGFR TKI treatment available for central confirmation of T790M.
- Measurable or evaluable disease
- Adequate haematological, renal and liver function
- Performance status 0-2

Exclusion criteria

- Patients with mixed NSCLC with predominantly squamous cell cancer, or with any small cell lung cancer (SCLC) component.
- Symptomatic or active central nervous system metastases, as indicated by clinical symptoms, cerebral edema, and/or progressive growth.
- Previous treatment with osimertinib and/or bevacizumab
- Patients currently receiving medications or herbal supplements known to be potent CYP3A4 inducers
- Any unresolved toxicities from prior therapy greater than CTCAE V 4.0 grade 1

Treatment arms:

Experimental arm: Osimertinib, 80 mg *p.o.*, once daily plus bevacizumab 15 mg/kg *i.v.* on day 1 of every 3-week cycle.

Control arm: Osimertinib, 80 mg *p.o.*, once daily

Patients will receive the treatment until progression, lack of tolerability, or patient declines further protocol treatment. Trial treatment may also continue beyond progression for as long as the patient may still derive benefit as per investigator decision.

Statistical considerations:

This superiority, multicentre trial compares PFS between the two randomised arms, and includes an interim analysis for the primary endpoint. A treatment effect on PFS, leading to a 36% reduction in HR is assumed under the alternative (HR=0.64). This improvement corresponds to an increase for the median PFS to 17.2 months under the combination treatment vs 11 months for the osimertinib treatment. A sample size of 154 patients (with 126 PFS events) is required for the trial to achieve 80% power to show a statistically significant difference in PFS for the assumed treatment effect at the 5% one-sided significance level.

Total trial duration: 5 years from enrolment of the first patient

2. List of abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
ALP	Alkaline Phosphatase
AST	Aspartate Transaminase
AT	Aminotransferase or Transaminase
AUC	Area Under the Curve
BID	Bis In Die (lat.), twice-daily
BOR	Best Overall Response
BORR	Best Overall Response Rate
CHF	Congestive Heart Failure
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
CVA	Cerebrovascular Accident
DCR	Disease Control Rate
DLCO	Diffusing Capacity for Carbon Monoxide
DVH	Dose Volume Histogramm
EC	Ethics Committee
eCRF	Electronic Case Report Form
ED	Extensive Stage Disease
EDC	Electronic Data Capture
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
ERB	Ethical Review Board
FVC	Forced Vital Capacity
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin Fixed, Paraffin Embedded
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
GTV	Gross Tumour Volume
Hb	Hemoglobin
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
IA	Iterim Analysis
IASLC	International Association for the Study of Lung Cancer
IB	Investigator's Brochure

IC	Informed Consent
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
INR	International Normalised Ratio
IMP	Investigational Medicinal Product
irAE	Immune-related Adverse Events
irBORR	Best Overall Response Rate by irRC
irPFS	Immune-related Progression Free Survival
IRB	Institutional Review Board
ITT	Intention-To-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
KDR	Kinase inert domain-containing receptor
LF	Lost to Follow-up
LFT	Liver Function Test
LLN	Lower Limit of Normal Lab Value
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MIP	Maximum Intensity Projection
MLD	Mean Lung Dose
MRI	Magnetic Resonance Imaging
MUGA	Multigated Acquisition Scan
NE	Not Evaluable
NCCN	National Comprehensive Cancer Network
NGS	Next Generation Sequencing
NSCC	Nonsquamous-Cell Carcinoma
NSCLC	Non-Small Cell Lung Carcinoma
OAR	Organs at Risk
ONJ	Osteonecrosis of the Jaw
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Cell Death Ligand 1
PFS	Progression Free Survival
PlGF	Placental Growth Factor
PIS	Patient Information Sheet
PK	Pharmacokinetics
PPK	Population Pharmacokinetic
PR	Partial Response
PRES	Posterior Reversible Encephalopathy Syndrome

PS	Performance Status
QD	Quaque Die, once daily
PTV	Planning Target Volume
RECIST	Response Evaluation Criteria in Solid Tumours
RT	Radiotherapy
SAE	Serious Adverse Event
SADR	Serious Adverse Drug Reaction
SBRT	Stereotactic Body Radiation Therapy
SCC	Squamous-Cell Carcinoma
SCLC	Small-Cell Lung Carcinoma
SD	Stable Disease
SIAD	Syndrome of Inappropriate Diuresis
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standard Uptake Volume
Tc99mDTPA	Technetium-99m Diethyl Triamine Penta-Acetic Acid
TdP	Torsades de Pointes
TE	Ttracheoesophageal
TIA	Transient Ischaemic Attack
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal Lab Value
VALG	Veterans Administration Lung Study Group
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell Count
WBRT	Whole Brain Radiotherapy
WC	Withdrawal of Consent

3. Trial schedule

	≤28 days before rando[1]	**Treatment period**				**PD**[7]	**End of treatment visit**	**Post treatment follow-up**	
		Control Arm[3]	Experimental Arm[4]	Prior to bevacizumab cycle 4 / at 9 weeks	Beyond PD[6]			Before PD[8]	After PD (every 12 weeks (±2 weeks)
Written informed consent: before any trial specific evaluations and intervention	within 6 weeks before rando								
Medical history: smoking history, comorbidities and allergies									
Physical examination[9]								PS, blood pressure, weight	
Resting 12-lead ECG[10]			Every cycle						
LVEF[11]		Every 15 weeks (±1 week)							
Ophthalmologic exam[12]		Repeated if patient experiences any visual symptoms							
Baseline symptoms									
Adverse events							Up to 30 days after trial treatment stop		
Concomitant medications[13]									
Survival									
Disease evaluation									
Radiological tumour assessment[14]	Within 5 weeeks before rando	Every 9 weeks (±4 days) until PD						Every 9 weeks (±4 days) until PD	
Confirmation of EGFRm[15]									
Confirmation of T790M[16]									
Biological material									
Tumour material	(17)					Optional			
Whole blood, serum and plasma samples	(17)			(5)					

Laboratory tests									
Pregnancy test for women of child bearing potential[18]									
Chemistry: serum albumin, glucose, potassium, sodium, calcium, amylase, lipase and LDH	(2)		Every cycle						
Haematology: haemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count)	(2)		Every cycle						
Liver function test: total bilirubin, ALT, AST, ALP, GGT	(2)		Every cycle						
Renal function tests: urea, uric acid, serum creatinine, creatinine clearance (Cockroft-Gault).	(2)		Every cycle						
Urine analysis: specific gravity, pH, proteins[19] using dipstick, glucose, blood using a dipstick; elements and microscopic examination if needed	(2)		Every cycle[19][19]						
Coagulation profile: international normalized ratio									
Treatment									
Osimertinib, daily 80mg *p.o.*, until PD, lack of tolerability or refusal[20] [21]									
Bevacizumab, 15 mg/kg *i.v.* every 3 weeks (±3 days) until PD, lack of tolerability or refusal[20] [22]									
Document further anti-cancer therapies after PD									

Mandatory evaluation / intervention

(1) Evaluations to be done within 28 days before randomisation. Examinations done prior to 28 days before randomisation have to be repeated.
(2) These evaluations have to be repeated within 7 days prior to trial treatment start
(3) Patients in the control arm: assessments have to be done every 3 weeks (±3 days).
(4) Patients in the experimental arm: assessments have to be done every 3 weeks (within 3 days prior to the next bevacizumab dose)
(5) Blood samples for translational research have to be collected within 3 days prior to cycle 4 (in the experimental arm) or 9 weeks (±1 week) after treatment start (in the control arm).
(6) In case of clinical benefit, with physician and patient agreement, trial treatment can continue beyond confirmed progression.
(7) Blood samples have to be taken at the time of tumour progression, a re-biopsy is voluntary.
(8) Patient who discontinues trial treatment before disease progression should be assessed every 9 weeks (±1 week) from end of treatment visit until tumour progression.
(9) Physical examination include: PS, blood pressure, heart rate, temperature, body weight, height (only at baseline), skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.
(10) Patients should be monitored for ECG changes at every cycle. ECGs should be reviewed and any abnormalities noted.
(11) LVEF should be measured at baseline, then at least every 15 weeks (±1 week) from the time of first dose of osimertinib throughout the treatment period and when clinically indicated. In the event of an absolute decrease of 10% from baseline or below 50%, withhold osimertinib for up to 4 weeks. If improved to baseline it can be restarted, but if not, then discontinue. It is up to the investigators choice to measure LVEF by either echocardiogram or MUGA scan. The same technique must be used for each patient throughout the treatment period.
(12) Full ophthalmic assessment, including slit lamp examination, should be performed at screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated.
(13) Information on any treatment within 28 days prior to starting trial treatment and all concomitant treatments given during the trial, with reasons for the treatment, will be recorded.
(14) Radiological tumour assessment by CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included) at baseline before randomisation and then every 9 weeks (63 ±4 days) from randomisation until PD determined according to RECIST v1.1 criteria.
(15) Histological or cytological confirmation of exon 19 deletion or exon 21 L858R mutation by a certified local laboratory.
(16) Confirmation of T790M mutation determined from biopsy (preferred) or on serum circulating tumour DNA by a certified local laboratory that performs this test within their routine practise. These samples must be taken after disease progression on the most recent EGFR TKI regimen.
(17) Whole blood, plasma, serum, and – if a biopsy was taken and the FFPE material is not yet fully depleted - tumour tissue/cytology after disease progression on the most recent EGFR TKI treatment administered prior to trial entry must be submitted for central confirmation of T790M and translational research studies. Submission of the same type of material as used for local identification of T790M is critical for central confirmatory analysis.
(18) Pregnancy test: Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine beta HCG pregnancy test within 7 days before randomisation. The test has to be repeated before treatment start, if treatment does not start within 72 hours of the previous test.
(19) Proteinuria should be routinely measured before every infusion of bevacizumab using a dipstick.
(20) Patients are considered to be on trial treatment for as long as they receive either osimertinib and/or bevacizumab
(21) Osimertinib treatment may continue beyond progression if the patient shows clinical benefit.
(22) Bevacizumab for patients in the experimental arm may continue beyond progression if the patient shows clinical benefit.

4. Background and rationale

4.1. Disease background

Lung cancer has been the most common carcinoma in the world for several decades. There were estimated 1.8 million new cases in 2012 (12.9% of the total). It is also the most common cause of death from cancer worldwide, estimated to be responsible for nearly one in five (1.59 million, 19.4% of the total deaths [1]).

Non-small cell lung carcinoma (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of NSCLC patients already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of early stage NSCLC patients who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer [2]. Patients presenting with unselected advanced NSCLC have a median overall survival of 10 to 12 months [3].

4.1.1. EGFR mutations

Progress in molecular biology has changed the therapeutic approach to NSCLC, and the treatment of advanced NSCLC can now be guided by the presence of certain mutations, eg, epidermal growth factor receptor (EGFR), or anaplastic lymphoma kinase (ALK). Since the discovery of the common somatic mutations in the kinase domain of EGFR in 2004 [4], it is now confirmed that NSCLC patients with activating EGFR mutations in exons 18 - 21 of EGFR (including L858R and exon 19 deletions, collectively described as EGFRm) are a distinct subset of NSCLC in terms of pathogenesis, prognosis and treatment.

EGFR tyrosine kinase inhibitors (TKIs) are now the established first line therapy in patients with EGFRm NSCLC (NCCN 2012 [5]). Despite achieving very good initial response rates and durable benefit following treatment with approved TKI drugs targeting EGFRm, these patients will eventually develop treatment-resistant disease after 9-14 months [6-12].

Survival rates of patients with advanced NSCLC who progress following treatment with EGFR-TKI remain very low, with a median overall survival of 1-2 years [13-15]. Treatment following progression on EGFR TKI therapy is guided by patient performance status, symptoms, and extent of disease. Patients have traditionally been treated with chemotherapy.

In patients able to tolerate platinum-containing doublet chemotherapy, this is most often the preferred second-line treatment. Second-line platinum-based chemotherapy post EGFR TKI for EGFRm NSCLC generally provides response rates in the range of 20 to 30% [7, 14-17]. The most robust estimate of ORR with platinum-containing doublet chemotherapy in the relevant patient population (ie, patients with EGFRm NSCLC after first-line EGFR TKI) comes from the recently reported IMPRESS study (ORR 25% with independent central review) [18]. Median PFS with platinum-containing doublet chemotherapy is generally reported to be in the range of 3-6 months (second-line), as was seen in the IMPRESS study (median 5.4 months).

Following progression on an EGFR TKI and doublet chemotherapy the only remaining options for patients with EGFRm NSCLC are to re-challenge with EGFR TKI, or to receive

salvage chemotherapy (usually single-agent) or investigational agents through clinical trials [19]. In the subset of patients who have failed prior platinum-containing doublet chemotherapy, studies in unselected patient populations highlight the low response rates (approximately 10%) and short PFS (median PFS approximately 2-3 months) expected with single-agent chemotherapy such as docetaxel, or pemetrexed [20-23] (and NCCN guidelines [24]). There are no robust data on treatment outcomes in EGFRm patients in this setting.

A number of mechanisms of resistance that lead to the EGFR TKI failure have been postulated, but the most frequently observed resistance mechanism is the emergence of the T790M mutation in EGFR, which is detected in the tumours of around 60% of patients after EGFR TKI failure [25-27]

There are currently no approved therapies that effectively address acquired resistance to EGFR TKI therapy as a result of the EGFR T790M mutation. However, a number of investigational agents that target both the EGFRm and T790M (TKI-resistance confering mutation) receptor forms of EGFR are currently under investigation in clinical trials, and two of these agents have shown promising efficacy in phase II studies following treatment of patients with locally advanced or metastatic EGFR T790M mutation positive NSCLC who have progressed on or after EGFR TKI therapy [28, 29].

4.1.2. Tumour angiogenesis

Vascular endothelial growth factor (VEGF) is a key angiogenic factor regulating angiogenesis, the growth of new vessels from pre-existing vessels. This process is fundamental to the growth of solid tumours, which rely on the formation of new blood vessels, and it plays a significant role in NSCLC; microvessel count is an independent predictor of poor prognosis in patients with NSCLC [30]. The VEGF family comprises in mammals five members: VEGF-A, VEGF-B, PIGF, VEGF-C and VEGF-D.

Two high-affinity receptors for VEGF with associated tyrosine kinase activity have been identified on human vascular endothelium: VEGFR-1 (Fms-like-tyrosine kinase-1 [Flt-1]) and VEGFR-2 (Kinase inert domain-containing receptor [KDR]). A third receptor, VEGFR-3 (Flt-4), is expressed on lymphatic endothelium. Although their relative contributions in mediating tumour progression have not been clearly understood, a number of studies suggest KDR performs a predominant role [31].

Clinically, the addition of anti-angiogenic agents to chemotherapy in the treatment of advanced NSCLC have led to OS benefit, and two such agents are now approved for this indication. The anti-angiogenic agent bevacizumab (a monoclonal antibody that inhibits VEGF-A), has been shown to provide additional efficacy when used in combination with first-line platinum-based chemotherapy in several trials in non-squamous NSCLC [32, 33]. Bevacizumab in combination with platinum based chemotherapy followed by maintenance bevacizumab is approved for first-line treatment of patients with advanced non-squamous NSCLC.

Increased production of VEGF has been reported to be associated with resistance to EGFR inhibition [34]. Pre-clinical studies suggest that erlotinib resistance may be associated with a rise in both tumor cell and host stromal VEGF and that combined blockade of the VEGFR and EGFR pathways can abrogate primary or acquired resistance to EGFR TKIs [35]. Pre-clinical studies also indicate that combination with anti-VEGF therapy could enhance

antitumor activity of anti-EGFR therapy and/or partially reverse resistance to EGFR TKI, by increasing EGFR TKI concentration in specific tumors that express high levels of VEGF protein [36].

4.2. Treatment background

4.2.1. Osimertinib

Osimertinib (AZD9291) is an oral, potent irreversible inhibitor, selective for the sensitizing EGFR mutations (EGFRm) and T790M resistance mutation with a significant selectivity margin against wild-type EGFR. This mono–anilino–pyrimidine compound is structurally distinct from other third-generation EGFR TKIs and offers a pharmacologically differentiated profile from earlier first and second generation EGFR TKIs [37].

Preclinically, the drug potently inhibits signaling pathways and cellular growth in both EGFRm and EGFRm plus T790M cell line *in vitro*, with lower activity against wild-type EGFR cell lines [38, 39].

Osimertinib is currently under investigation as a treatment option in: 1) Patients with advanced T790M positive NSCLC who have previously failed an EGFR-TKI; 2) Patients with advanced EGFRm NSCLC who are treatment naïve; 3) In combination with novel agents for patients with EGFR TKI resistant NSCLC.

In the phase 1 dose escalation trial of osimertinib (D5160C00001, AURA), no dose-limiting toxicities were reported in any of the dose escalation cohorts (20, 40, 80, 160, and 240 mg) and a non-tolerated dose has not been defined. Based on all currently available safety, pharmacokinetic and preliminary efficacy data, 80 mg once daily was selected as the recommended phase II dose.

Data from the ongoing phase I AURA trial (D5160C00001) in patients with T790M positive NSCLC who were previously treated with EGFR TKI, have achieved promising efficacy with osimertinib; 54.2%, with 95% CI (40.8% - 67.3%) of subjects achieved a response, 91.5%, with 95% CI (81.3% - 97.2%) achieved disease control, medium duration of response of 12.4 months 95%, with 95% CI (8.3 - NC) and median PFS based on 38% maturity of data was 13.5 months, with 95% CI (8.3 - NC), as assessed by blinded independent central review [28]. Promising evidence of efficacy has also observed in patients with EGFRm treatment naïve NSCLC treated with osimertinib as first line EGFR TKI (Abstract ASCO 2015 [40]).

Across the clinical development programme, osimertinib has demonstrated a manageable safety profile [28].

4.2.2. Bevacizumab

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the interaction of VEGF-A to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour

vasculature, thereby inhibiting tumour growth. Administration of bevacizumab to xenotransplant models of colon cancer in nude mice caused reduction of microvascular growth and inhibition of metastatic disease progression [41, 42].

Bevacizumab is indicated for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non–squamous NSCLC in combination with carboplatin and paclitaxel. The recommended dose of bevacizumab in this indication is 15 mg/kg by *i.v.* infusion once every 3 weeks (Bevacizumab Investigator's Brochure (IB).

4.3. Overall risk / benefit assessment

4.3.1. Potential benefits

Osimertinib monotherapy, at the dose to be evaluated in this trial, has shown consistent and high objective response rates in the target patient population (see Section 4.2.1).

Anti-angiogenic agents targeting the VEGF/VEGFR signaling pathway have been shown to provide additional efficacy when used in combination with first-line platinum-based chemotherapy in several trials in non-squamous NSCLC or in combination with erlotinib as first line therapy in EGFRm positive NSCLC patients (see Section 4.2.2).

The combination of osimertinib plus an anti-angiogenic agent such as bevacizumab may provide a wider activity against tumours that have developed resistance to EGFR TKI agents by blocking the dual pathways of proliferative signaling and angiogenic signaling. Preclinical studies suggested that patients on lower doses of EGFR TKI tend to develop treatment resistance earlier than those who receive higher doses [43]. Therefore the combination may also delay the development of subsequent resistance as the preclinical studies suggested anti-angiogenic agents may increase intratumoural uptake of anti-cancer drugs by changing tumour vessel physiology [44].

Efficacy and safety data from the osimertinib monotherapy studies have shown promising efficacy and an acceptable safety profile (Section 11.1) at the recommended dose of 80 mg once daily. The combination of osimertinib with bevacizumab may have the potential to provide additional clinical benefit in terms of increased and/or prolonged disease control and a delay in the emergence of resistance in patients with advanced EGFRm NSCLC who have progressed following a prior EGFR TKI agent, compared against the current standard of care (chemotherapy or another EGFR TKI) or monotherapy of any of the individual agents.

4.3.2. Potential risks

Section 10.7 of this protocol summarizes potential risks based upon non-clinical toxicity and clinical patient studies with osimertinib or bevacizumab with further detailed information available in the respective IBs for osimertinib and bevacizumab. As these agents have not previously been administered in combination, although the chances are low based upon the associated preclinical and clinical evidence, there is a theoretical potential for synergistic toxicity to occur, beyond that described for monotherapy administration.

4.4. Rationale for trial design, doses and control groups

A combination strategy for the angiogenesis inhibitor bevacizumab has been explored in a randomised, open-label phase II trial of erlotinib in combination with bevacizumab versus erlotinib alone as first-line therapy in patients with EGFRm NSCLC [45]. The results yielded a significantly extended progression-free survival (PFS); median PFS in the combination therapy group was 16 months, vs. 9.7 months in the erlotinib alone group, for a hazard ratio of 0.54 (95% CI 0.36 - 0.79; P = .0015). Those with exon 19 deletion had a median PFS of 18 months with the combination therapy compared with 10.3 months with erlotinib alone (HR = 0.41; 95% CI, 0.24 - 0.72). Those with exon 21 L858R mutation, however, had a median PFS of 13.9 months with bevacizumab and 7.1 months without it (HR = 0.67; 95% CI, 0.38 - 1.18). The overall survival data is still immature, but the magnitude of PFS benefit suggests it may translate into an overall survival benefit. Fewer patients progressed after response with the combination, suggesting that bevacizumab may act to enhance the durability of response and cause sustained tumor shrinkage.

More recently, the ETOP 2-11 BELIEF trial examined the same combination in patients with advanced NSCLC and activating EGFR mutations [46]. In this open-label, phase II trial, the combination of bevacizumab and erlotinib was explored in 109 patients with metastatic or locally advanced, non-squamous NSCLC who were not candidates for radical surgery or radiotherapy.

Patients had measurable disease and centrally confirmed activating *EGFR* mutations (exon 19 deletion or *L858R* mutations). All patients were treated with intravenous bevacizumab at 15 mg/kg on day 1 of each 3-week cycle, and oral erlotinib at 150 mg daily.

Pre-treatment T790M mutations were centrally identified based on laser micro-dissection and TaqMan assays in the presence of a specific peptide–nucleic acid to inhibit the amplification of the wild-type allele. DNA from PC9 cells containing an ultra-low allele frequency (0.004%) of T790M mutation were used as negative and NCI-H1975 (T790M) cells as positive controls. With this sensitive PC9 cutoff method, the presence of T790M at diagnosis was documented in 37 (34%) of the 109 recruited patients with classical activating EGFR mutations. The median age of patients with T790M-mutated NSCLC was 70 years, 68% were female, 73% were never smokers, and 95% had ECOG PS 0-1. Patients without the alteration were at median age of 63 years, 58% were female, 63% never smokers, and 94% had ECOG PS 0-1.

At a median follow-up of 17.5 months, 36 patients remained on treatment (17 with a T790M mutation and 19 without).

The combination of erlotinib and bevacizumab resulted in an overall 1-year PFS of 56.7% (95% CI, 46.0 - 66.0) and a median PFS of 13.8 months (95% CI, 10.3 - 21.3). In patients that did not have the T790M alteration at diagnosis, the 1-year PFS was 49.4% (95% CI, 36.6 - 61.0) and the median PFS 10.5 (95% CI, 9.2 - 16.2),, while the 1-year PFS was 72.4% (95% CI, 53.4 - 84.7) and the median PFS 16.0 months (95% CI: 13.1 - NE) in patients with documented T790M mutation at diagnosis [46].

The safety profile of the combination was consistent with that of each agent and no unexpected toxicities were identified.

The results from these two studies suggest that combination treatments that target both tumour cells and tumour microenviroment (such as angiogensis) may be a promising strategy for further improving efficacy outcomes in patients with EGFRm NSCLC following progression on EGFR TKI therapy and other lines of therapy.

First-generation EGFR TKI provide significant clinical benefit in patients with advanced EGFRm NSCLC [10, 12, 47]. However, all patients ultimately develop disease progression, driven – as the most prevalent identified biological mechanism – by the acquisition of a second T790M EGFR TKI resistance mutation [48-50].

There is thus a considerable unmet clinical need for novel therapeutic options that can further extend the efficacy of targeted agents such as EGFR TKIs, across all lines of therapy.

4.4.1. Rationale for patient selection

To ensure an appropriate and standardised patient population, all patients must have documented radiological progression on EGFR-TKI treatment and on the last treatment administered prior to enrolling in the trial. A biopsy (preferred) or blood sample will be needed for central testing of T790M mutation status following confirmed disease progression on the most recent treatment regimen.

4.4.2. Rationale for osimertinib dose

In the phase I dose escalation trial of osimertinib (D5160C00001, AURA), once daily doses of 20, 40, 80, 160, and 240 mg osimertinib were evaluated. Based on the total, current, safety, pharmacokinetic and preliminary efficacy data, 80 mg once daily was selected as the recommended phase II dose. The dose of 80 mg osimertinib daily can be reduced to 40 mg osimertinib once daily under circumstances described in Section 10.5. Further dose reductions are not possible. Please refer to the Osimertinib IB for additional details. No dosage adjustment is required due to patient age, body weight, gender, ethnicity and smoking status.

5. Objectives and endpoints

5.1. Primary objective

To assess the efficacy of the combination of osimertinib and bevacizumab versus osimertinib alone in terms of progression-free survival (PFS) assessed by RECIST 1.1.

5.2. Secondary objectives

To compare short and long term clinical efficacy outcomes as well as tolerability of the two treatments.

5.3. Primary endpoint

5.3.1. Progression-free survival (PFS) based on RECIST 1.1 criteria

5.4. Secondary endpoints

5.4.1. Objective response, based on RECIST 1.1 criteria

5.4.2. Disease control, defined as complete or partial response, or disease stabilisation, confirmed at subsequent radiological assessment

5.4.3. Adverse events graded by CTCAE V4.0

5.4.4. Overall survival

5.5. Correlative studies

5.5.1. T790M evolution in tissue and plasma/serum (between baseline and relapse)

5.5.2. Monitoring of mutation burden and specific EGFR mutations (del19, L858R, T790M) in sequential plasma/serum samples

5.5.3. Analysis of bevacizumab/osimertinib resistance mechanism in relapse biopsy samples (NGS)

6. Trial design, duration and termination

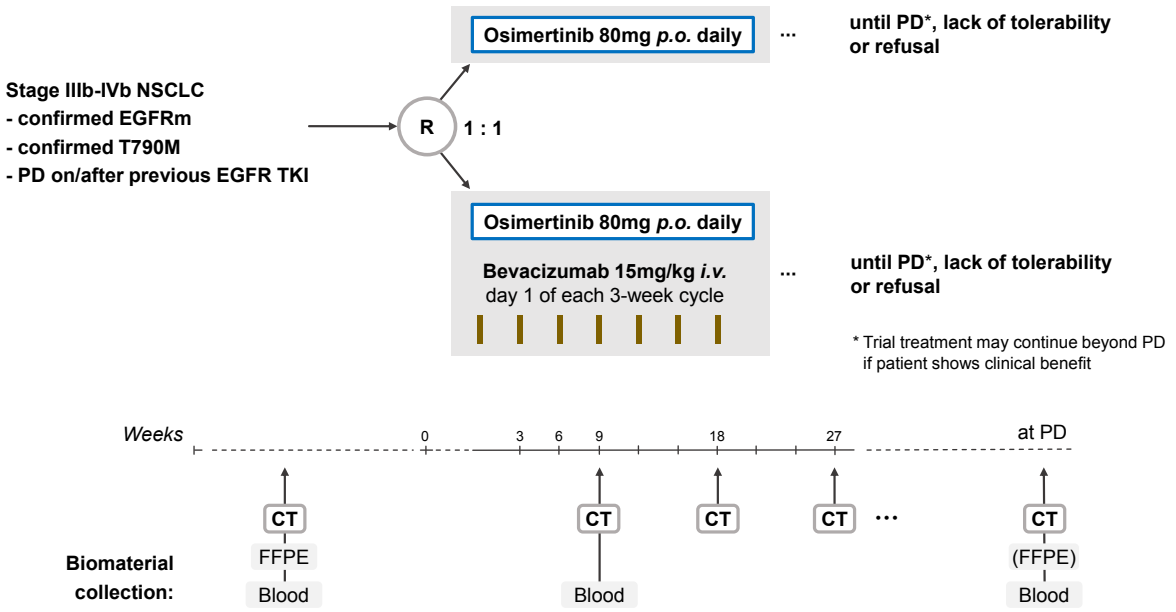
This is a randomised controlled phase II multinational, multi-center trial of osimertinib and bevacizumab versus osimertinib alone as second-line treatment in patients with stage IIIb-IVb NSCLC harbouring activating EGFR (exon 19 deletion or L858R) and T790M resistance mutation.

6.1. Trial design

This is a randomised phase II trial, with block stratified randomisation balanced by institution with a total of 154 patients randomised 1:1 to the experimental and control arm.

Stratification factors:

Ethnicity (Asian, Non-asian) and material used for T790M (tumour vs circulating DNA)



6.2. Sample size and trial duration

The total sample size of 154 randomised patients is needed in order to observe the 126 events required to detect a 36% improvement in PFS under the combination of osimertinib and bevacizumab with 80% power at the 5% one-sided significance level. Thus, in this phase II trial, 77 patients will be randomised into each of the two treatment arms.

The recruitment is assumed to be non-linear with recruitment rate increasing to 6 per month, after the first 6 months. The required total trial follow-up duration is expected to be 48 months with an interim efficacy analysis based on O'Brien-Fleming boundary at 26 months. Estimating a run-in period of 6 months, and a 6-month preparation of the report, the total trial duration is expected to be 5 years.

The 154 patients will be recruited from 25 centres in 6 different countries in Europe and Asia.

7. Patient selection

Written informed consent (IC) must be signed and dated by the patient and the investigator prior to any trial-related intervention and biomaterial submission for central review and testing.

7.1. Inclusion criteria

7.1.1. Patients (male/female) must be ≥18 years of age.

7.1.2. NSCLC, stage IIIb/IIIc (not amenable to radical therapy) or IVa/IVb according to 8th TNM classification, after progression following prior EGFR TKI therapy (erlotinib, gefitinib, dacomitinib or afatinib) as the most recent treatment regimen.

7.1.3. Pathological diagnosis of predominantly non-squamous NSCLC.

7.1.4. Maximum one line of previous platinum based chemotherapy.

7.1.5. Histological or cytological confirmation of EGFRm (exon 19 deletion or exon 21 L858R).

7.1.6. Locally confirmed T790M mutation determined from biopsy (preferred) or on circulating tumour DNA, documented in tissue, plasma or serum after disease progression on the most recent treatment regimen.

7.1.7. Plasma, serum, and tumour (preferred) tissue or cytology (if biopsy was taken and FFPE tumor material is not yet fully depleted) after disease progression on the most recent EGFR TKI treatment available for central confirmation of T790M.

7.1.8. Measurable or evaluable disease according to RECIST 1.1

7.1.9. Adequate haematological function:

- Haemoglobin ≥90 g/L
- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
- Platelet count $\geq 100 \times 10^9$/L

7.1.10. Adequate renal function:

- Creatinine ≤1.5 × ULN OR
- Creatinine clearance ≥30 mL/min (using the Cockroft-Gault formula below). **Cockroft-Gault formula**

$$\frac{\text{mL}}{\text{min}} = \frac{(140\text{-age[years]}) \times \text{actual body weight [kg]}}{72 \times \text{Creatinine}_{\text{serum}} \left(\frac{\text{mg}}{\text{dL}}\right)} \ (\times 0.85 \text{ if female})$$

- Proteinuria <2+ (dipstick)

7.1.11. Adequate liver function:

- ALT and AST ≤2.5 × ULN. If the patient has liver metastases, ALT and AST must be ≤5 × ULN
- Total bilirubin ≤1.5 x ULN. If the patient has liver metastases or documented Gilbert's syndrome (unconjugated hyperbilirubinaemia) ≤3 x ULN.

7.1.12. World Health Organization (WHO) performance status 0-2

7.1.13. Life expectancy ≥12 weeks

7.1.14. Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine pregnancy test within 7 days before randomisation.

7.1.15. Patient is willing and able to comply with the protocol for the duration of the trial including undergoing treatment and scheduled visits and examinations including follow up.

7.1.16. Written Informed Consent (IC) for trial treatment must be signed and dated by the patient and the investigator prior to any trial-related evaluation and/or intervention and biomaterial submission for central review.

7.2. Exclusion criteria

7.2.1. Patients with mixed NSCLC with predominantly squamous cell cancer, or with any small cell lung cancer (SCLC) component.

7.2.2. Symptomatic or active central nervous system metastases, as indicated by progressive growth or increasing need of steroids. Patients with history of CNS metastases or spinal cord compression are eligible if they are clinically and radiologically stable for at least 4 weeks before first dose of investigational product and have not required high-dose steroid treatment (>20mg prednisone or equivalent) in the last 4 weeks.

7.2.3. Patients currently receiving (or unable to stop within 3 weeks before receiving the first dose of trial treatment) medications or herbal supplements known to be potent inducers of CYP3A4 (see section 10.4.1). Patients currently receiving phenobarbitone must stop this treatment within 5 weeks before receiving the first dose of trial treatment). All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer/inhibitory effects on CYP3A4 during trial treatment.

7.2.4. Any unresolved toxicities from prior therapy greater than CTCAE V 4.0 grade 1 at the time of starting trial treatment with the exception of alopecia and grade 2, prior platinum-therapy related neuropathy.

7.2.5. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol, or active infection including hepatitis B, hepatitis C and HIV. Screening for chronic conditions/infections is not required.

7.2.6. Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis requiring steroid treatment, or any evidence of clinically active ILD.

7.2.7. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib.

7.2.8. Any of the following cardiac criteria:

- Mean resting corrected QT interval (QTc using Fredericia's formula) >470 msec, obtained from 3 ECGs, using the screening clinic ECG machine derived QTc value.
- Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block or second degree heart block).

- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medication known to prolong the QT interval.

7.2.9. Previous history of significant hemoptysis (defined as at least 2.5mL emission of red blood) in the 3 months prior to inclusion.

7.2.10. Recent surgery:

- Major surgery or significant traumatic injury within 28 days prior to inclusion
- Minor surgical procedure within 7 days, or placement of a vascular access device within 2 days of study enrolment.

7.2.11. Previous treatment with bevacizumab.

7.2.12. Previous treatment with osimertinib.

7.2.13. Women who are pregnant or in the period of lactation.

7.2.14. Sexually active men and women of childbearing potential who are not willing to use an effective contraceptive method during the trial and up to 6 months after discontinuing trial treatment (see Section 10.7.1).

8. Patient screening and randomisation

8.1. Screening

Complete the following steps to screen and include a patient into this trial. Please consult the ***BOOSTER procedures manual*** for detailed instructions.

Note that written informed consent has to be obtained from the patient prior to any trial-specific intervention or submission of biomaterial for central review.

Verify eligibility and randomise the patient in the EDC system ETOPdata according to the information in the ***BOOSTER procedures manual***. The dates the patient signed informed consent to enter the trial and to pathology material submission as well as the dates the investigator signed those forms are all required to complete the eligibility checklist.

8.2. Randomisation and stratification

Patients will be randomly assigned (1:1) to receive either osimertinib plus bevacizumab or osimertinib alone.

Block stratified randomisation [51] balanced by institution will be performed centrally, stratified by ethnicity (Asian vs non-Asian) and material used for T790M testing (tumour, circulating DNA) (tumour vs circulating DNA). Blocks will be multiples of two (block size either 4 or 6), randomly generated.

All patients and investigators will be unmasked to the trial treatment.

9. Investigational medicinal products

Osimertinib and bevacizumab are the investigational medicinal products (IMPs) in this trial.

Complete details of the IMP logistics, distribution, packaging, labeling and handling as well as accountability are described in the ***BOOSTER drug supply manual***.

9.1. Osimertinib

Osimertinib is an oral, potent irreversible inhibitor, selective for sensitizing (EGFRm) and T790M resistance mutation with a significant selectivity margin against wild-type EGFR. As a result, osimertinib can effectively block EGFR signaling both in EGFR single mutant cells with activating EGFR mutations and in double mutant cells bearing the T790M resistance mutation. Osimertinib is currently under investigation as a treatment option in:

1) Patients with advanced T790M positive NSCLC who have previously failed an EGFR-TKI;

2) Patients with advanced EGFRm NSCLC who are treatment naïve, and,

3) In combination with novel agents for patients with EGFR TKI resistant NSCLC.

Please refer to the Osimertinib IB for details of the clinical programme for osimertinib.

9.1.1. Formulation

Investigational product	Dosage form and strength	Manufacturer
Osimertinib	40 mg tablets 80 mg tablet	AstraZeneca

AstraZeneca will supply osimertinib as tablets for oral administration. Osimertinib will be supplied in bottles with 25 tablets per bottle. Additional information about pharmaceutical formulation may be found in the current version of the Osimertinib IB.

9.2. Bevacizumab

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the interaction of VEGF-A to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth. Please refer to the current Avastin IB for details. Bevacizumab will be supplied by Roche.

9.2.1. Formulation

Clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (*i.v.*) infusion

9.3. Packaging and labeling

Clinical supplies will be affixed with a clinical trial label in accordance with regulatory requirements.

9.4. Clinical supplies disclosure

This trial is open-label; therefore, the patient, the trial site personnel, ETOP and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text.

9.5. Storage and handling

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

The investigational product label on the bottle and concentrate and the Investigator Brochures (IBs) specify the appropriate storage.

10. Trial treatments

10.1. Overview trial treatment

Experimental arm: Osimertinib, 80 mg *p.o.*, once daily plus bevacizumab 15 mg/kg *i.v.* on day 1 of every 3-week cycle.

Control arm: Osimertinib, 80 mg *p.o.*, once daily

Patients will receive the trial treatment until progression, lack of tolerability to osimertinib and bevacizumab, or patient declines further protocol treatment. Trial treatment may also continue beyond progression for as long as the patient may still derive benefit as per investigator decision.

10.2. Osimertinib

Osimertinib is administered as 80 mg once daily. Osimertinib can be taken without regard to food.

Doses should be taken approximately 24 hours apart at the same time point each day with water. Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the scheduled dose, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their osimertinib, they should not make up for this dose, but should take the next scheduled dose.

The dose of 80 mg osimertinib daily can be reduced to 40 mg osimertinib once daily under circumstances described in Section 10.5. Further dose reductions are not possible. Once a dose has been reduced, it should not be re-escalated at future cycles. Any change from dosing schedule, dose interruptions, or dose reductions should be recorded.

10.3. Treatment compliance

Osimertinib will be given in accordance with the protocol and the instructions of a site investigator or pharmacist.

The appropriate number of osimertinib tablets will be provided to patients to be self-administered at home. Patients should be instructed to use the patient diary to record every self-administration as well as any symptoms and to bring the patient diary to every visit at the clinic.

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

The investigator and/or ETOP can withdraw a patient from the trial in the event of serious and persistent non-compliance which jeopardizes the patient's safety or render trial results for this patient unacceptable. Patients who do not attend a minimum of 75% of scheduled

trial visits, unless due to exceptional circumstances, should be discussed with ETOP and be evaluated for compliance.

10.4. Prohibited and restricted concomitant therapies during treatment with osimertinib

Information on any treatment within 28 days prior to starting trial treatment and all concomitant treatments given during the trial (and up to 30 days after end of trial treatment), with reasons for the treatment, will be recorded. If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see below), should be maintained on it throughout the study period. Guidance on medicines to avoid, medications that require close monitoring and on washout periods while the patient is receiving osimertinib is provided below.

10.4.1. Strong CYP3A inhibitors/inducers

Based on *in vitro* data and predicted clinical exposure data, osimertinib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. *In vitro* data have shown that the principal CYP enzymes responsible for the phase I metabolism of osimertinib are CYP2C8 and CYP3A4.

The contribution of phase I metabolism to the total clearance of osimertinib is currently unknown but, to ensure patient safety, the following potent inhibitors and inducers of CYP2C8 and CYP3A4 must not be used during this trial for any patient receiving osimertinib.

<u>CYP3A inducers:</u>

The concurrent use of CYP3A inducers, including carbamazepine, phenobarbital, phenobarbitone, phenytoin, rifabutin, rifampicin, rifapentin, and St. John's wort, are not allowed in the trial and withdrawal period prior to osimertinib start is 3 weeks for all the above except phenobartitone, the withdrawal period prior to starting osimertinib treatment is 5 weeks).

10.4.2. Drugs known to prolong QT interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with osimertinib. Recommended withdrawal periods prior to osimertinib start with these agents are provided in the Table 1.

Table 1: Drugs prolonging QT interval

Contraindicated drug	**Withdrawal period**
Clarithromycin, droperidol, erythromycin, procainamide	2 days
Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozide	4 weeks

Arsenic trioxide	6 weeks*
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

10.4.3. Other concomitant medications

- Statins: Up to 1.5-fold increase in statin exposure may occur when coadministered with osimertinib. It is recommended that the starting and maintenance dose of statins should be as low as possible and should be guided by the statin prescribing information. Monitoring of low density lipoprotein (LDL) cholesterol levels is advised. If the patient experiences any potentially relevant adverse events suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, the statin should be stopped, creatine kinase (CK) levels should be checked, and any appropriate further management should be taken.
- Patients taking warfarin should be monitored regularly for changes in prothrombin time or international normalized ratio (INR).
- Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE V 4.0 grade ≤2) while receiving treatment with osimertinib until at least one week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE V 4.0 grade ≥3) ocular events, they must discontinue wearing their contact lenses until at least one week after treatment with osimertinib is permanently discontinued. Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed to by the investigator, at any time during the access program until 1 week after osimertinib has been permanently discontinued. Patients should consult their clinician promptly if they have any concerns.

10.5. Management of osimertinib related toxicities

If a patient experiences a grade 3 or higher and/or unacceptable toxicity (any grade), where the clinician considers the event of concern to be specifically associated with osimertinib (and not attributable to the disease or disease-related processes for which patient is being treated), dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. Detailed information on the clinical management of events may be found in the appendix 2 (Guidance for the management of adverse events in studies of osimertinib).

If the toxicity resolves or reverts to grade ≤2 within 3 weeks of onset, trial treatment may be restarted at the same dose (starting dose) or at a reduced dose of 40 mg osimertinib at the investigator's discretion and with discussion and agreement with ETOP medical review if needed.

If the toxicity does not resolve to grade ≤2 after 3 weeks, then the patient will be permanently withdrawn from the study treatment after discussion and agreement with ETOP medical review and observed until resolution of the toxicity. There will be no individual

modifications to the treatment schedule in response to toxicity, only potential dose reduction or dose interruption.

Dose adjustments and interventions for adverse events should be in accordance with Table 2 and Table 3.

Table 2: Osimertinib dose adjustment information for adverse reactions

Target Organ	**Adverse reaction**(*)	**Dose modification**
Pulmonary	ILD/Pneumonitis (grade ≥3)	Permanently discontinue osimertinib
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg).
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Other	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks
	If grade 3 or higher adverse reaction improves to grade 0-2 after withholding of osimertinib for up to 3 weeks	osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to grade 0-2 after withholding for up to 3 weeks	**Permanently discontinue osimertinib**

(*) Graded by CTCAE V 4.0.

Table 3: Osimertinib dose interventions

	osimertinib dose
Starting Dose	80 mg daily
Reduced Dose	40 mg daily

If an event subsequently requires dose interruption, osimertinib may restart at the same dose or the reduced dose, on resolution/improvement of the event at the discretion of the clinician. Once a dose has been reduced, it should not be re-escalated at future cycles.

10.5.1. Interstitial lung disease/pneumonitis

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in osimertinib dosing is recommended, and ETOP medical review (Medical.Affairs@ibcsg.org) should be informed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative

causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage.

Where ILD is suspected, administer corticosteroids at a dose of 1 – 2 mg/kg/day prednisone equivalents for grade 2 or greater pneumonitis, followed by corticosteroid taper.

In the absence of a diagnosis of ILD osimertinib may be restarted.

A diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, laboratory parameters) should be performed, to exclude conditions such as lymphangitic carcinomatosis, infection, allergy or pulmonary haemorrhage.

In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded a diagnosis of interstitial lung disease should be considered and trial treatment permanently discontinued.

10.5.2. Left ventricular ejection fraction (LVEF)

Osimertinib and its active metabolite may also inhibit HER2. For this reason:

- Measurement of LVEF should be performed if the investigator has clinical suspicion of new onset impaired cardiac function
- Consult cardiologist for abnormal LVEF results, at the investigator's discretion
- Patients are to be managed clinically according to standard of care

10.5.3. QTc Prolongation

Patients with QTc prolongation (i.e., confirmed QTc prolongation to >500 msec absolute or a > 60 msec increase from baseline) should have osimertinib treatment interrupted and regular ECGs performed until resolution to baseline.

If the toxicity resolves or reverts to grade ≤2 within 3 weeks of onset, treatment with osimertinib may be restarted at the same dose (80 mg, daily) or a lower dose (40 mg, daily) using the rules for dose modifications (see also appendix 2, "Guidance for the management of adverse events in studies of osimertinib").

If the toxicity does not resolve to grade ≤2 after 3 weeks, then the patient should be withdrawn from the trial and observed until resolution of the toxicity.

10.5.4. Ophtalmic adverse events

There is a known association between the use of EGFR TKIs and the occurrence of ophthalmic adverse events.

Patients on EGFR TKIs, including osimertinib, should be

- Fully informed that ophthalmic events may occur during treatment with osimertinib
- Monitored periodically for these events
- Osimertinib should not be administered on the first scheduled day if the patient has any clinically significant eye symptoms.

- Patients should be encouraged to report any instances of ophthalmic symptoms and/or vision changes to allow the appropriate treatment to be initiated. Symptoms may include:
  - Burning / itching / irritation / smarting
  - Redness with / without discharge
  - Blurred vision
  - Light sensitivity

Patients who wear contact lenses must discontinue wearing them if:

- They have any mild to moderate eye symptoms (CTCAE V 4.0 grade ≤2) until at least one week after symptoms have resolved.
- They have a recurrence of eye symptoms or experience any severe (CTCAE V 4.0 grade ≥3) ocular events until at least one week after treatment with osimertinib is permanently discontinued.

Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by treating physician, at any time during the trial until one week after osimertinib has been permanently discontinued.

10.5.5. Corneal Ulceration

Patients experiencing corneal ulceration will not be permitted to restart osimertinib treatment.

10.5.6. Skin reactions

Skin effects may occur at any time, but are most likely to start within 2 weeks of commencing treatment.

- Patients may consider applying over-the-counter moisturising cream to face, hands and feet twice daily from the start of treatment with osimertinib.
- Physicians may consider issuing a prescription to patients for topical treatment. However, topical steroids and topical or oral antibiotics should not be implemented prophylactically and treatment should only be started when confirmed by the treating physician.
- As soon as an acneiform / papulopustular rash occurs, treatment with moderate strength topical steroids and antibiotics should be implemented.
- The occurrence of non-papulopustular skin reactions should be treated appropriately, as defined by the treating physician, and in consultation with a dermatologist where necessary.
- Use of topical benzoyl peroxides and other irritating anti-acne agents should be avoided.
- Patients should be fully informed regarding skin reactions:
  - may occur during treatment with osimertinib

    - skin reactions are not contagious, and
    - do not result from allergy to treatment
- may consider applying over-the-counter moisturising cream to face, hands and feet bid from the start of treatment
- to contact the site to report any instances of skin reaction as soon as they arise so that appropriate treatment can be promptly initiated
    - and, especially if the skin reaction changes (e.g. if it spreads or becomes painful)
- It may be beneficial to avoid irritating skin products (e.g. irritating soaps, products containing retinol or retinoic acid)
- Camouflage make-up (non-comedogenic or non-pore blocking) can be used during treatment.

10.5.7. Diarrhea

Patients should be fully informed that diarrhea may occur during treatment with osimertinib and that diarrhea is not contagious, and does not result from allergy to treatment. Patient should contact the site to report any instances of diarrhea as soon as they arise so that appropriate treatment can be promptly initiated.

Recommendations for appropriate management of diarrhea, including dose-adjustments for adverse events of diarrhea that are of grade ≥ 3 or that are clinically significant and/or intolerable and considered by the clinician to be causally related to osimertinib, is provided in Appendix 2, "Guidance for the Management of Adverse Events in Studies with osimertinib".

10.6. Bevacizumab

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

- Blood pressure should be routinely measured before every infusion and after a resting period of 10 min.
- Proteinuria should be routinely measured before every infusion of bevacizumab using dipstick.
- No routine premedication (e.g. to prevent infusion reaction) is recommended for bevacizumab.

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

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

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

10.6.1. Management of bevacizumab related toxicities

Treatment with bevacizumab should be temporarily interrupted if one of the following adverse events occurs despite optimal supportive care, when not attributable to the disease under investigation, where the investigator considers the AE of concern to be specifically associated with bevacizumab:

- Any intolerable adverse event regardless of grade
- Any adverse events CTCAE V 4.0 grade ≥3 (despite optimal supportive care)

If toxicity resolves or reverts to CTCAE V4.0 grade ≤1 within 21 days of onset and the patient is showing clinical benefit, treatment with bevacizumab may be restarted using the rules below for dose modifications and with discussion and agreement with ETOP medical review (Medical.Affairs@ibcsg.org) as needed.

If toxicity does not resolve to CTCAE V 4.0 grade ≤1 after 21 days, then the patient should be withdrawn from the trial and observed until resolution of the toxicity.

There are no recommended dose reductions. Bevacizumab should be discontinued in the event of GI perforation, fistula, reversible posterior leukoencephalophathy syndrome (RPLS) and wound healing complications.

The bevacizumab-related AEs hypertension, proteinuria, thromboembolism and hemorrhage indlucing any CNS bleeding, as well as any grade 3 or 4 bevacizumab related AEs, should be managed as described below.

Hypertension

Table 4: Management of bevacizumab-related hypertension

	Description	**Actions**
Grade 1	Prehypertension (systolic BP 120 to 139 mmHg or diastolic BP 80 to 89 mmHg)	No bevacizumab dose modification
Grade 2	Stage 1 hypertension (systolic BP 140 to 159 mmHg or diastolic BP 90 to 99 mmHg); recurrent or persistent (≥24 hours); symptomatic diastolic BP increase by >20 mmHg; monotherapy indicated	Start anti-hypertensive therapy. Once blood pressure is <150/100 mmHg, patients may continue bevacizumab therapy
Grade 3	Stage 2 hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg); more than one drug or more intensive therapy than previously used indicated	Hold bevacizumab for persistent or symptomatic hypertension and discontinue permanently if hypertension is not controlled
Grade 4	Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Permanently discontinue bevacizumab

Proteinuria

Table 5: Management of Proteinuria

	Description	Action
Grade 1	Urine dipstick 1+ or urine protein level 0.15 - 1.0 g/24 hrs	No bevacizumab dose modification
Grade 2	Urine dipstick 2+ to 3+ or urine protein level >1 - 3.5 g/24 hrs	Suspend bevacizumab for ≥2 g/24 hrs and resume when proteinuria is <2 g/24 hrs For 2+ dipstick: May administer bevacizumab, obtain 24 hour urine prior to the following dose of bevacizumab For 3+ dipstick: Obtain 24 hour urine prior to administration
Grade 3	Urine dipstick 4+ or urine protein level >3.5 g/24 hrs	Suspend bevacizumab. Resume when proteinuria is <2 g/24 hrs, as determined by 24-hrs urine collection <2 grams.
Grade 4	Nephrotic syndrome	Permanently discontinue bevacizumab

Thrombosis/Embolism

- Arterial thromboembolism (ATE, including pulmonary embolism):

  Permanently discontinue bevacizumab for any grade ATE;

- Venous thromboembolism (grade ≥3)
  - First occurrence: discontinue bevacizumab, until toxicity has improved to grade≤1 within 21 days;
  - Second occurrence: permanently discontinue bevacizumab.

Hemorrhage

- 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: permanently discontinue bevacizumab.
- Grade 3 or 4 bleeding of any other kind: permanently discontinue bevacizumab.

Surgery and wound healing complications

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

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

Temporarily suspend bevacizumab for:

- At least 4 weeks prior to elective surgery
- First venous thromboembolic event grade 3 or 4 requiring full anticoagulation; bevacizumab may be resumed after initiation of therapeutic-dose anticoagulant therapy if the patient is on a stable dose of anticoagulant
- Severe hypertension not controlled with medical management. Blood pressure should be less than 150 mmHg systolic and 100 mmHg diastolic before bevacizumab is given. If blood pressure is higher, measurement should be repeated and if hypertension is confirmed, antihypertensive medication should be started and bevacizumab should be delayed until blood pressure drops below 150/100 mmHg.
- Proteinuria grade 3; resume bevacizumab once grade 2 or less has been attained.
- Grade 3 or 4 bevacizumab-related events (except grad 3 hypertension) occurring for the first time: bevacizumab should be discontinued until toxicity improves to grade 1. When a grade 3 o 4 occurs for second time, bevacizumab should be discontinued permanently

Discontinue bevacizumab for:

- Arterial thromboembolism (any grade)
- Febrile grade 4 neutropenia and/or grade 4 thrombocytopenia regardless of the relationship to treatment
- Grade ≥3 venous thrombosis/embolism (including pulmonary embolism) and recurrent venous thromboembolic event requiring full anticoagulation
- Gastrointestinal perforations (gastric ulcer, fistula formation in the gastrointestinal tract, intra-abdominal abscess)
- Grade ≥2 fistula formation involving an internal organ
- Cerebral or cardiac ischemic events
- Grade ≥3 left ventricular dysfunction (CHF)
- Wound dehiscence and wound healing complications requiring medical intervention
- Nephrotic syndrome.
- CNS bleeding (any grade) or grade ≥3 bleeding of any kind
- Grade >=2 hemoptysis

- Medically significant hypertension not controlled with antihypertensive therapy, hypertensive crisis or hypertensive encephalopathy
- Posterior reversible encephalopathy syndrome (PRES)
- Severe infusion reactions
- Recurring grade 3 or 4 bevacizumab-related event
- A treatment delay of more than 6 weeks

10.7. Contraception, nursing, pregnancy

10.7.1. Contraception

Female patients who are not of childbearing potential due to being postmenopausal (2 year without menstruations) or surgically sterilised (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception to be eligible for the trial. All other female patients are considered to be of childbearing potential.

Women of childbearing potential and sexually active men must use highly effective contraception from the start of treatment with osimertinib and bevacizumab and until 6 months after the last dose. The following contraception methods are considered highly effective:

- Hormonal (estrogen and progesterone) contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation
- Progesterone-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation
- Intrauterine deviced (IUD) or intrauterine hormone releasing systems (IUS)
- Bilateral tubal occlusion
- Vasectomy

Women who become pregnant while participating in the trial must discontinue trial medication immediately. The pregnancy must be reported following procedures detailed in Section 12.12. Also any pregnancy that occurs in a female partner of a male trial participant must be reported.

Patients should be informed that taking the trial medication may involve unknown risks to the fetus if pregnancy were to occur during the trial. In order to participate in the trial they must adhere to the contraception requirement (described above) for the duration of the trial up to 6 months after the last dose of any trial treatment. If there is any doubt whether a patient will reliably comply with the requirements for contraception, that patient should not be entered into the trial.

10.7.2. Use in pregnancy

If a patient inadvertently becomes pregnant while on trial treatment, trial treatment will be stopped immediately for the patient and the event reported immediately, see Section 12.12. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to ETOP without delay and within 24 hours if the outcome is a serious adverse

experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The trial investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to ETOP.

10.7.3. Use in nursing women

It is unknown whether osimertinib or bevacizumab is excreted in human milk. Since maternal IgGs and many drugs are excreted in milk and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for randomisation.

10.8. Treatment duration

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

- Documented progression according to RECIST v1.1, except if the patient may still derive benefit as per investigator's decision.
- Unacceptable toxicity to either osimertinib or bevacizumab
- Medical condition that prevents further treatment
- Patient withdraws consent
- Patient becomes pregnant
- Trial termination (e.g. approximately 18 months after randomisation of the last patient).

11. Safety of trial treatments

Clinical experience with osimertinib is described in the current version of the Osimertinib Investigator's Brochure.

11.1. Safety profile of osimertinib

11.1.1. Potential risks with osimertinib

Important treatment emergent adverse events associated with the monotherapy administration of osimertinib include diarrhoea, rash/acne and dry skin. Other potential EGFR-TKI class-related effects include corneal ulceration, liver transaminases increases and ILD, although none of these events are currently considered to be associated with administration of osimertinib. As of the cut-off of 19 November 2013 there have been 5 reports of unconfirmed ILD-like events identified in the ongoing study. Assessment of causality is complicated by the diagnosis of advanced NSCLC, including prior treatments, which are known to pre-dispose patients to occurrence of ILD.

Based on the identified and potential risks associated with osimertinib treatment, this trial protocol incorporates mandatory safety monitoring procedures and guidance to assist with

early diagnosis and rapid management of potential osimertinib drug-related symptoms. Dose modification algorithms are also included in this protocol.

11.1.2. Known adverse reaction

The following CTC v 4.0 grade 3 - 5 adverse reactions have been reported:

Very common (≥10%): diarrhoea, rash and acne, dry skin, stomatitis, nail effects, leucopenia, thrombocytopenia, neutropenia

Common (1 – <10%): rash and acne, dry skin, stomatitis, ILD, nail effects

Uncommon (0.1% - <1%): QTc prolongation (grade 3; >500 ms QTcF)

11.1.3. Contraindications

Osimertinib is contraindicated in individuals who are hypersensitive to any component of the finished dosage forms.

11.1.4. Gastrointestinal tract effects including stomatitis

Diarrhoea is the most commonly reported AE with osimertinib, reported at a frequency of very common (>10%). The majority of reported AEs of diarrhoea were considered mild or moderate in severity. AEs of diarrhoea were rarely reported as grade ≥3 and did not generally lead to discontinuation of osimertinib.

There were no reports of haemorrhagic diarrhoea or GI perforation in phase I or II studies.

Stomatitis has been reported by NSCLC patients in clinical trials with osimertinib during the reporting period, at a frequency between 5.5% and 13.7% across dose levels, with most events mild in severity and a small number of moderate cases. Only 1 patient experienced a grade ≥3 event. There is an upward inflection in the incidence of stomatitis between 80 mg and 160 mg. The impact of stomatitis on patients receiving osimertinib, as measured by numbers of SAEs (including hospitalisations) and dose modifications or discontinuations is low.

Patients with refractory nausea, vomiting and chronic gastrointestinal diseases are excluded from participating in studies. Detailed information on the treatment of gastrointestinal adverse events are described in section 10.5 and are included in the “guidance for the management of adverse events in studies of osimertinib” (appendix 2).

11.1.5. Dermatological events and nail disorders

Dermatological events such as rash, acne and dry skin have occurred in the osimertinib clinical studies at a frequency of common (>1% and <10%) to very common (>10%) across dose levels. Most events were CTCAE V 4.0 grade 1. Nail effects have previously been identified as a potential risk of treatment with osimertinib as a known class effect for EGFR inhibitors. Nail effects is a group term of closely related events, which includes changes to the nail and nail bed which have been reported at all doses of osimertinib in clinical trials. The highest incidence has been seen at the highest doses of osimertinib and the incidence ranges from 25.1% for the 80 mg dose to 50.0% for the 240 mg dose. Nail effects have been

mostly mild (grade 1) or moderate (grade 2) in severity. There has been one severe event (paronychia, grade 3) for which dosing was interrupted.

There are no specific dermatological exclusion criteria. However, patients with any unresolved adverse event from prior therapy greater than grade 1 will be excluded from participating in studies. Dermatological treatment should be instituted for patients with any skin reactions, considered by the investigator to be causally related to osimertinib. Detailed information on the treatment of dermatological adverse events is included in the "guidance for the management of adverse events in studies of osimertinib" (appendix 2).

11.1.6. Ocular surface effects

There is no evidence of a causal relationship between osimertinib and ocular surface effects.

Full ophthalmic assessment, including slit lamp examination, will be performed at screening and should be repeated if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE.

Any patient developing corneal ulceration will be permanently discontinued from trial treatment and should be followed regularly until resolution of the event.

Patients who wear contact lenses should discontinue wearing lenses if they have any mild to moderate eye symptoms (grade ≤2) while receiving treatment with osimertinib until at least one week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (grade ≥3) ocular events they should discontinue wearing their contact lenses until at least one week after treatment with osimertinib is permanently discontinued. Patients should not use any eye drops or ointment for treatment of eye symptoms, unless agreed by the investigator, at any time during the trial until 1 week after osimertinib has been permanently discontinued. Patient will be advised to consult the clinic promptly if they have any concerns.

11.1.7. Cardiac Contractility

There is no evidence of a causal relationship between osimertinib and decrease in cardiac function or cardiac contractility. In the phase II pooled population, of 375 patients who had post-baseline echocardiography assessment, an LVEF decrease from baseline of ≥10 percentage points to an LVEF value <50% occurred in 2.4% (9/375) of patients.

Additionally, an LVEF increase from baseline of ≥10 percentage points occurred in 9.9% (37/375) of patients. Evaluation of LVEF measurement during the treatment period did not identify any clinically significant change in median values over time, and there is no suggestion that osimertinib causes an adverse reaction on cardiac contractility.

11.1.8. QTc

Across AURA phase I and II; and AURA2, an increase in QTcF interval compared with baseline was observed, with a median increase of approximately 15 msec, at steady state on day 1 of cycle 3 but with no evidence that this is associated with an increased risk of cardiac arrhythmias or TdP.

In AURA2 an intensive assessment of ECG parameter was performed addressing key aspects of a conventional thorough QT/QTc study, including time-matched ECG assessments, to enable evaluation of any pro-arrhythmic risk of osimertinib.

The mean time-matched change from baseline in QTcF at week 6 across all time points was 14.5 ms (90% CI 14.0 - 15.0), with the maximum upper 90% CI limit at any time point being 17.5 ms.

In AURA2, based on the time-matched pre-dose baseline and post-dose ECG samples with post-dose PK sampling at the same time points, the mean (90% CI) increase in ΔQTcF interval was estimated to be 0.271 (90% CI: 0.241 - 0.301) msec per 10 nM-increase in osimertinib plasma levels, based on a linear mixed effects model, with gender not having a significant effect in the model. Based on this concentration QTc analysis, the predicted drug related QTc interval prolongation at the proposed osimertinib therapeutic dose (80 mg) is 14.2 msec (upper bound of 90% CI: 15.8 msec).

This magnitude of effect exerted by osimertinib is considered to be of limited clinical significance as evidenced by the low number of AEs reported under the QT prolongation SMQ in the phase II studies - 17 (4.1%) patients with ECG QT prolonged: 9 (2.2%) patients had AEs that were maximum grade 1, 3 (0.7%) patients had AEs that were maximum grade 2, and 5 (1.2%) patients had AEs that were maximum grade 3.

11.1.9. Respiratory effects, including ILD

Like many EGFR inhibitors, osimertinib is associated with ILD. In the phase II studies (AURA extension and AURA2), at the DCO date of 01 May 2015 ILD (grouped terms) was reported in 2.7% (11/411) of patients during treatment with osimertinib 80 mg in the phase II studies. The median time to onset for ILD grouped term events in the phase II studies was 83 days (range 17 to 230 days).

Considering the importance of ILD as an event, an additional analysis has been conducted, which includes other ongoing studies with osimertinib, at a DCO date of 01 June 2015. At this date, osimertinib had been dosed to 1221 patients across the clinical development programme. A total of 2.9% (35/1221) patients have reported ILD or suspected ILD-like events.

11.2. Safety profile of bevacizumab

11.2.1. Potential risks with bevacizumab

Warnings and precautious for bevacizumab include perforation or fistula; surgery and wound healing complications; hemorrhage; arterial thrombembolic events; venous thromboembolic events; hypertension; posterior reversible encephalopathy syndrome (PRES); proteinuria; infusion reactions; ovarian failure. The most common adverse reactions observed in bevacizumab patients at a rate >10% and at least twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis (see SPC for details).

In a phase II study of erlotinib in combination with bevacizumab as first line therapy for EGFRm NSCLC patients, no new safety signals were identified between erlotinib plus bevacizumab group and erlotinib alone group, with hypertension (60% vs 10%) and proteinuria (8% vs 0%) being the more frequently observed grade 3 AEs in the combination group compared against erlotinib alone group [45].

Based on the identified and potential risks associated with bevacizumab, this trial protocol incorporates mandatory safety monitoring procedures and guidance to assist with early diagnosis and rapid management of potential drug-related symptoms.

11.2.2. Known adverse reactions

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

Very common (≥10%): Febrile neutropenia, leucopenia, thrombocytopenia, neutropenia, anorexia, peripheral sensory neuropathy, dysarthria, headache, dysguesia, eye disorder, lacrimeation icreased, hypertension, thromboembolism, dyspnoea, rhinitis, rectal haemorrhage, stomatitis, constipation, diarrhoea, nausea, vomiting, absominal pain, wound healing complications, exfoliative dermatitis, dry skin, skin discoloration, arthralgia, proteinuria, ovarian failure, asthenia, fatigue, pyrexia, pain, mucosal inflammation, weight decreased.

Common (1 – <10%): Sepsis, abscess, cellulitis, infection, urinary tract infection, anaemia, lymphopenia, hypersensitivity, infusion reaction, dehydration, cerebrovascular accident, syncope, somnolence, headache, congestive heard failure, supraventricular tachycardia, arterial thromboembolism, deep vein thrombosis, haemorrhage, pulmonary haemorrhage, haemoptysis, pulmonary embolism, dysphonia, hypoxia, epistaxis, gastrointestinal perforation, intestinal perforation, ileus, intestinal obstruction, recto-vaginal fistulae, gastrointestinal disorder, proctalgia, palmar-plantar erythrodysaesthesia syndrome, fistula, muscular weakness, myalgia, back pain, pelvic pain, lethargy.

11.2.3. Contraindications

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

11.2.4. Special warnings and precautions for use

Gastrointestinal (GI) perforations and fistulae

Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with bevacizumab. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Prior radiation is a risk factor for GI perforation in patients treated for persistent, recurrent or metastatic cervical cancer with bevacizumab and all patients with GI perforation had a history of prior radiation. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

GI-vaginal fistulae

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab are at increased risk of fistulae between the vagina and any part of the GI tract (Gastrointestinal-vaginal fistulae). Prior radiation is a major risk factor for the development of GI-vaginal fistulae and all patients with GI-vaginal fistulae had a history of prior radiation. Recurrence of cancer within the field of prior radiation is an additional important risk factor for the development of GI-vaginal fistulae.

Non-GI fistulae

Patients may be at increased risk for the development of fistulae when treated with bevacizumab. Permanently discontinue bevacizumab in patients with tracheoesophageal fistula 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.

Wound healing complications

Bevacizumab may adversely affect the wound healing process. Serious wound healing complications, including anastomotic complications, with a fatal outcome have been reported. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery.

Necrotising fasciitis

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

Hypertension

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

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics

to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. 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.

Posterior Reversible Encephalopathy Syndrome (PRES)

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

Proteinuria

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that all grade proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with bevacizumab. Therapy should be permanently discontinued in patients who develop nephrotic syndrome.

Arterial thromboembolism

In clinical trials, the incidence of arterial thromboembolic reactions including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone.

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

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

Venous thromboembolism

Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under bevacizumab treatment.

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab in combination with paclitaxel and cisplatin may be at increased risk of venous thromboembolic events.

Bevacizumab should be discontinued in patients with life-threatening (grade 4) thromboembolic reactions, including pulmonary embolism. Patients with thromboembolic reactions ≤ grade 3 need to be closely monitored.

Haemorrhage

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

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

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

Pulmonary haemorrhage/haemoptysis

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

Congestive heart failure (CHF)

Reactions consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with bevacizumab.

Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

In patients in AVF3694g who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all grade CHF was observed in the

anthracycline + bevacizumab group compared to the treatment with anthracyclines only. CHF grade 3 or higher reactions were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment.

Neutropenia and infections

Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone. This has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC, metastatic breast cancer, and in combination with paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.

Hypersensitivity reactions/infusion reactions

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

Osteonecrosis of the jaw (ONJ)

Cases of ONJ have been reported in cancer patients treated with bevacizumab, the majority of whom had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when bevacizumab and intravenous bisphosphonates are administered simultaneously or sequentially.

Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with bevacizumab. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible.

Intravitreal use

Bevacizumab is not formulated for intravitreal use.

Eye disorders

Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of bevacizumab compounded from vials approved for intravenous administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased,

intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.

Systemic effects following intravitreal use

A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors.

Ovarian failure/fertility

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

11.2.5. Elderly Patients

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

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

12. Adverse event and serious adverse event reporting

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

The main criterion for tolerability is the occurrence of toxicities and adverse events. The severity and causality will be classified according to the CTCAE version 4.0. The CTCAE is available for downloading on the internet at http://evs.nci.nih.gov/ftp1/CTCAE/About.html. An interactive version can be found at https://safetyprofiler-ctep.nci.nih.gov/.

12.1. Adverse event (AE)

An adverse event (AE) is defined as any untoward medical occurrence that occurs from the date of signature of informed consent until 30 days after all trial treatment discontinuation, regardless of whether it is considered related to a medication.

Any grade of any observed AE should be reported on the AE eCRFs.

12.2. Adverse reaction (AR)

An adverse reaction (AR) is defined as “any noxious and unintended response to an IMP related to any dose administered”.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship (see Section 12.8) to an IMP qualify as adverse reactions. The expression suspected/related means to convey in general that there is evidence or argument to suggest a causal relationship to the trial treatment.

12.3. Unexpected adverse reaction (UAR)

An unexpected adverse reaction (UAR) is any adverse reaction, the nature, or severity of which is not consistent with the applicable product information.

When the outcome of the adverse reaction is not consistent with the IB or summary of product characteristics (SPC) this adverse reaction should be considered as unexpected.

12.4. Serious adverse events (SAE)

A serious adverse event (SAE) is defined as any undesirable medical occurrence/adverse drug experience that at any dose:

- results in death (any cause, except progression of cancer under study)
- is life-threatening
- requires or prolongs inpatient hospitalisation
- results in persistent or significant disability/incapacity
- constitutes an important medical event
- is a congenital anomaly or birth defect (including neonatal deaths)
- is a secondary malignancy (see 0)
- is an event of clinical interest (see 12.4.4)

12.4.1. Inpatient hospitalisation

A hospital stay equal to, or greater than, 24 hours. Hospitalisations occurring under the following circumstances are **not** considered to be SAEs:

- elective surgery, for pre-existing conditions and planned prior to trial entry
- occur on an outpatient basis and do not result in admission (hospitalisation <24h)
- are part of the normal treatment or monitoring of the studied treatment

12.4.2. Important medical events

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalisation, or disability, but may jeopardise the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

12.4.3. Secondary malignancies

Primary malignancy

A second primary malignancy is one that is unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

12.4.4. Events of clinical interest (ECI)

The following events of clinical interest (ECIs) are not necessarily SAEs, but should be reported as such on the SAE eCRFs (***SAE Initial Reports***) by indicating that this is an "event of special interest".

- **Drug induced liver injury (DILI):** AST or ALT elevations ≥3x ULN with concurrent elevation of total bilirubin ≥2× ULN and, at the same time, alkaline phosphatase (AP) <2 × ULN.
- **Overdose**: All overdose with and without an AE must be reported by the investigator to ETOP safety office within 24 hours.

12.4.5. Osimertinib overdose

Osimertinib overdose is defined as any dose received above the protocol-mandated dose of 80 mg once daily.

There is no known antidote to osimertinib and there are no definitions regarding what constitutes an overdose. Investigators will be advised that any patient who inadvertently receives a higher dose than stated in the protocols should be treated with appropriate supportive care until recovery and followed up carefully.

12.4.6. Bevacizumab overdose

The highest dose tested in humans (20 mg/kg of body weight every 2 weeks *i.v.*) was associated with severe migraine in several patients. In the event of overdose, bevacizumab should be discontinued and the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

12.4.7. Exceptions to the SAE definition

The following situations do not need to be reported as SAEs:

- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalisation which was planned before the patient consented for trial participation and where admission did not take longer than anticipated (see also 12.4.1).
- A hospitalisation planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (serious) AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen significantly.
- Progression of cancer under study:

  By convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, unless the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

12.5. Serious adverse reaction (SAR)

A serious adverse reaction (SAR) is defined as any SAE which is considered related to the protocol treatment.

12.6. Suspected unexpected serious adverse reaction (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) occurring in clinical investigations qualify for expedited reporting to the appropriate regulatory authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

12.7. Severity / intensity of (serious) adverse events

The (serious) AE severity grade provides a qualitative assessment of the extent or intensity of a specific event, as determined by the investigator or as reported by the patient. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure), and does not reflect the relationship to trial drug. A severe event may be of relatively minor medical significance (such as severe headache). The term "severe" is **not** the same as "serious", which is based on patient/event **outcome** or **action criteria** associated with events that pose a threat to a patient's life or functioning.

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

- **Grade 1** = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- **Grade 2** = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- **Grade 3** = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisation is possible
- **Grade 4** = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalisation or hospice care probable
- **Grade 5** = Death – the event results in death

12.8. Causality of adverse events

The investigator must determine the relationship between the administration of trial drug(s) and the occurrence of an AE/SAE following the definitions indicated below:

Not suspected — The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected — The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Relationship to the protocol treatment	
Not suspected	**Suspected / related to trial treatment**
- unrelated - unlikely	- possible - probable - definite

12.9. Duration of adverse events

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

12.10. Action taken

The investigator will report the action taken with trial drug(s) because of an AE or SAE, as applicable (e.g. discontinuation of trial drug(s), medication needed for the treatment of an AE) and in case of an SAE report if concomitant and/or additional treatments were given for the event.

12.11. Reporting SAEs

Any SAE, whether related to trial drug or not, occurring in a patient after providing written informed consent (IC) must be reported, which occurs within 30 days following cessation of treatment or until the initiation of a new anticancer therapy, whichever is earlier. Information about all such events will be collected and recorded on the SAE eCRFs (***SAE Initial Reports***).

After completion of trial treatments, report all SAEs beyond 30 days that are considered at least possibly related to previous trial treatment. Cases of secondary malignancies and congenital abnormalities and neonatal deaths are to be considered as SAEs, regardless of whether they occur during or after trial treatment. These events should be reported during the whole trial duration on the serious adverse event eCRFs (***SAE Initial Reports***)

To ensure patient safety, ETOP must be informed of each SAE using the procedures described below:

- Any SAE must be reported by submitting the completed ***SAE Initial Reports*** eCRF in English within 24 hours of awareness in the EDC system ETOPdata.
- Queries may be issued by the ETOP safety office; a timely response by the investigator to all SAE-related queries is crucial.
- The SAE outcome must be reported within 15 days after initial reporting by online submitting the ***SAE Follow-up Report*** eCRF. In case the SAE is reported as ongoing after 15 days, a second follow-up report has to be submitted with the final outcome.

Submission of SAE is done via the EDC system, or in case of unavailability, by sending the SAE form by fax to the ETOP safety office:

+41 31 389 92 29

As soon as the EDC system is available again, the SAE eCRF has to be completed and submitted by the site.

The ETOP safety office will inform AstraZeneca and Roche safety and other appropriate persons about all SAEs within 24 hours of receipt at the ETOP safety office.

The ETOP safety office will review the SAE and prepare a summary report of all SAEs received. Listings of SAEs will be prepared as required.

12.12. Pregnancy

Patients who are not of childbearing potential due to being postmenopausal (2 years without menstruation) or surgical sterilisation (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception to be eligible for the trial. All other patients are considered to be of childbearing potential and must use adequate contraception throughout the trial.

Women of childbearing potential and sexually active men must use highly effective contraception during trial treatment and until 6 months thereafter. Please refer to section 10.6.1 for highly effective contraception methods.

12.12.1. Maternal exposure

In the case of pregnancy occurring during the course of the trial or within 6 months after treatment discontinuation, the investigator shall immediately (within 24 hours after awareness of pregnancy) notify ETOP by completing the pregnancy eCRF in ETOPdata in accordance with the SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported (within 14 days) by submitting a second pregnancy eCRF in ETOPdata. All neonatal deaths that occur within 30 days of birth should be reported, irrespective of causality, as SAEs. In addition, any infant death after 30 days, irrespective of causality should also be reported within 24 hours of the investigator's knowledge of the event using the SAE forms.

12.12.2. Paternal exposure

Pregnancy that occurs in a female partner of a male trial participant is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to during the course of the trial or within 6 month after treatment discontinuation by completing the pregnancy eCRF in ETOPdata.

12.13. Reference safety information

The osimertinib IB (IB AZD9291 edition 6, January 2016) section 5.4 and Avastin IB (IB 24 version November 2016) appendices 11 and 12 served as reference documents for the protocol.

For the determination of the expectedness of the serious adverse events of osimertinib and bevacizumab, the current versions of the IBs serve as reference safety information.

13. Response evaluation

13.1. CT schedule for response evaluation

Radiological tumour assessment by CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included) will be done at baseline within 6 weeks before randomisation.

CT scans will be repeated every 9 weeks (63 ±4 days) from randomisation until progression of disease determined according to RECIST v1.1 criteria. The same imaging technique, acquisition, and processing parameters should be used in a patient throughout the trial.

13.2. Response evaluation criteria in solid tumours (RECIST version 1.1)

13.2.1. Introduction

All included patients will be evaluated for disease response and progression according to the revised response evaluation criteria in solid tumours (RECIST version 1.1) [52].

In this trial, patients must have **measurable or evaluable** disease (see definitions below).

13.2.2. Methods of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumour effect of a treatment.

CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. CT scan should generally be performed using a ≤ 5 mm contiguous reconstruction algorithm. MRI is acceptable for certain situations, e.g. body scans.

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules) and ≥10 mm. In the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scan is preferable.

Ultrasound is not useful in assessment of lesion size and is not accepted as a method of assessment.

FDG-PET is not foreseen for regular response assessments. It may, however, be used to detect or confirm the appearance of new lesions. Attenuation correction CT scans performed as part of a PET/CT scan frequently show lower resolution; therefore, dedicated CT scans are preferred. However, if the site can demonstrate that the CT scan performed as part of a PET/CT is of the same diagnostic quality as a diagnostic CT scan (with *i.v.* and oral contrast), then the CT scan portion of the PET/CT can be used for RECIST measurements.

13.2.3. Measurable disease

Measurable disease is defined as the presence of at least one measurable lesion.

Measurable lesions:

- Tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5mm)
  - 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

  Reminder: A lesion in a previously irradiated area is not eligible for measurable disease.
- **Malignant lymph nodes**: to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan, assuming the slice thickness is ≤ 5 mm. At baseline and in follow-up, only the short axis will be measured.

13.2.4. Non-measurable disease

Non-measurable disease is defined as lesions or sites of disease that cannot be measured. Non-measurable lesions/sites of disease and special considerations:

- Small non-nodal lesions (longest diameter < 10 mm in CT scan)
- Small lymph nodes (short axis ≥ 10 and < 15 mm). Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed as measurable or non-measurable disease.
- Bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.
- Leptomeningeal disease
- Ascites
- Pleural or pericardial effusion
- Lymphangitic involvement of skin or lung
- Cystic lesions. Cystic lesions thought to represent cystic metastases may be considered as measurable lesions. However, if non-cystic lesions are present, these are preferred as target lesions

- Tumour lesions situated in a previously irradiated area, or subjected to other locoregional therapy. Such lesions may be considered measurable if there has been demonstrated progression in the lesion
- Abdominal masses/abdominal organomegaly identified by physical exam that are not measurable by reproducible imaging techniques

13.2.5. Selection of target lesions

Target lesions should be identified, measured and recorded at baseline. At baseline, there can be up to a maximum of 5 lesions representative of all involved organs, and up to 2 per organ. Target lesions should be selected on the basis of their size and their suitability for accurate repetitive measurements. A sum of diameters for all target lesions will be calculated and reported as the baseline sum of diameters. **Lymph nodes** selected as target lesions should always have the **short axis** recorded. All **other lesions** should always have their **longest diameters** recorded. The sum of diameters will be used as reference to further characterize the objective tumour response of the measurable dimension of the disease.

13.2.6. Selection of non-target lesions

All other lesions (or sites of disease) not identified as target lesions should also be recorded as non-target lesions at baseline.

For non-target lesions, measurements are not required, but the presence or absence of each should be noted throughout follow-up. It is possible to record multiple non-target lesions as a single item on the eCRF.

13.2.7. Evaluation of target lesions

All target lesions will be measured at each tumour assessment, and the sum of their diameters will be compared to previous assessments in order to assign the response status as specified below.

- Complete Response (CR): Disappearance of all target lesions. Lymph nodes selected as target lesions must each have reduction in the short axis to < 10 mm in order for the response to be considered complete. In this case, the sum of diameters may be > 0.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.
- Progression (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on the trial. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions (see section 13.2.9) denotes disease progression.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters recorded on the trial.

Note: All target lesions, including lymph nodes, should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist does not feel comfortable assigning an exact measure and reports a lesion as "too small to measure", a default value of 5 mm should be recorded. If a target lesion is thought likely to have disappeared, use "0 mm."

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

13.2.8. Evaluation of non-target lesions

- Complete Response (CR): Disappearance of all non-target lesions; lymph nodes selected as non-target lesions must be non-pathological in size (< 10 mm).
- Non-CR/non-PD: Persistence of one or more non-target lesions (non-CR).
- Progression (PD): unequivocal progression of existing non-target lesions. Unequivocal means: comparable in magnitude to the increase that would be required to declare PD for measurable disease, or an overall substantial increase in tumour burden that merits treatment discontinuation.

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

13.2.9. Determination of new lesions

The appearance of any new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal, i.e. not attributable to differences in scanning technique or findings thought to represent something other than tumour. If a new lesion is equivocal, e.g. because of its small size, the patient will stay on treatment (if the decision on PD is based on this lesion only). If the repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the previous scan when the lesion was discovered.

Lesions or sites of disease found in a new location not included in the baseline scan (e.g. brain metastases) are considered new lesions. The detection of new lesions is not restricted to the examination methods used at baseline.

Note: the "re-appearance" of a previously "disappeared" target or non-target lesion does not in itself necessarily qualify as PD; this is the case only if the overall evaluation meets the PD criteria, or if the patient was previously in CR.

13.2.10. Additional considerations

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

13.2.11. When the patient has only non-measurable disease

This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. 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 tumour 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’ or an increase in lymphangitic disease from localised to widespread. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II of reference [52].

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 increasemust be substantial.

13.2.12. Determination of time point response

Based on the responses of target lesions, non-target lesions, and the presence or absence of new lesions, the overall response will be determined at each tumour evaluation time point, according to the table below.

13.2.13. For patients with measurable disease

Table 6: Measurable Disease - Overall Response

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

*Non-CR/non-PD should be used rather than SD for categorizing non-target lesions.

13.2.14. For patients with non-measurable disease

Table 7: Non-measurable Disease - Overall Response

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR / non-PD*	No	Non-CR / non-PD*
Not evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

*Non-CR/non-PD should be used rather than SD for categorizing non-target lesions.

13.2.15. Determination of best overall response

Best overall response is defined as best response recorded from the start of treatment across all time points until disease progression. Confirmation of partial or complete response by an additional scan is not requested in this trial.

13.2.16. Storage of images

All CT images must be stored locally in electronic format for later central review, please consult the ***BOOSTER procedures manual*** for detail.

14. Endpoints definition

14.1. Progression-free survival

PFS, the primary endpoint, is defined as the time from the date of randomisation until documented progression (based on RECIST 1.1 criteria) or death, if progression is not documented. Censoring (for patients without a PFS/death event) will occur at the last tumour assessment if patient is lost to follow-up or refuses further documentation of follow-up.

14.2. Objective response

Objective response is defined as best overall response (CR or PR) across all assessment time-points according to RECIST criteria v1.1 (see section 13.2.14.), during the period from randomisation to termination of trial treatment.

14.3. Disease control

Disease control is defined as complete or partial response, or disease stabilisation, confirmed at subsequent radiological assessment.

14.4. Toxicity

Adverse events classified according to CTCAE version 4.0.

14.5. Overall survival

OS is defined as time from the date of randomisation until death from any cause. Censoring will occur at the last follow-up date.

15. Biological material and translational research

15.1. Central Histology Review, Biomarker Testing and Biobanking

A biobank for all biological material collected from every patient randomised in this trial will be created with centralised samples for translational research, integral to the trial. The required pathological material (described below) is submitted to, catalogued, and maintained at the Central Laboratory: Tumour tissue blocks, whole blood, serum and plasma samples will be centrally collected and biobanked at the central reference laboratory in Lausanne (Center for Experimental Therapeutics CTE, University of Lausanne, Switzerland). The material will be centrally archived, and subjected to central histology review and biomarker testing. Eventually, the biological material will be made available for translational research, following completion of the primary trial translational research objectives.

Translational research will encompase, but is not limited to, sequencing of most relevant oncogenes as well as EGFR/VEGFR pathways components will be retrospectively analysed on the tumour samples and compared to circulating surrogates in serum/plasma. Extension to a larger panel of genes by NGS (up to whole genome) on the tumour and on the serum/plasma might be performed and compared to germline DNA in whole blood. Potientially, gene expression analyisis on tumour and circulating RNA might be added to this project, depending on current lung cancer biology knowledge at the time of analysis.

15.2. Required biomaterial

Whole blood, plasma, serum, and – if a biopsy was taken and the FFPE material is not yet fully depleted - tumour tissue/cytology after disease progression on the most recent EGFR TKI treatment administered prior to trial entry must be submitted for central confirmation of T790M and translational research studies. Submission of the same type of material as used for local identification of T790M is critical for central confirmatory analysis.

15.2.1. Tumour tissue (if a biopsy was done after disease progression on the most recent treatment regimen)

Formalin-fixed, paraffin embedded (FFPE) tumour material (tissue or cytology) after disease progression on the most recent treatment regimen:

- FFPE tumour/cytology block (preferred) or
- alternatively 10 tissue sections of 4 (-5) µm thickness
- 10 slides cut from cytoblocks are acceptable only if tissue is not available and rebiopsy is not feasible

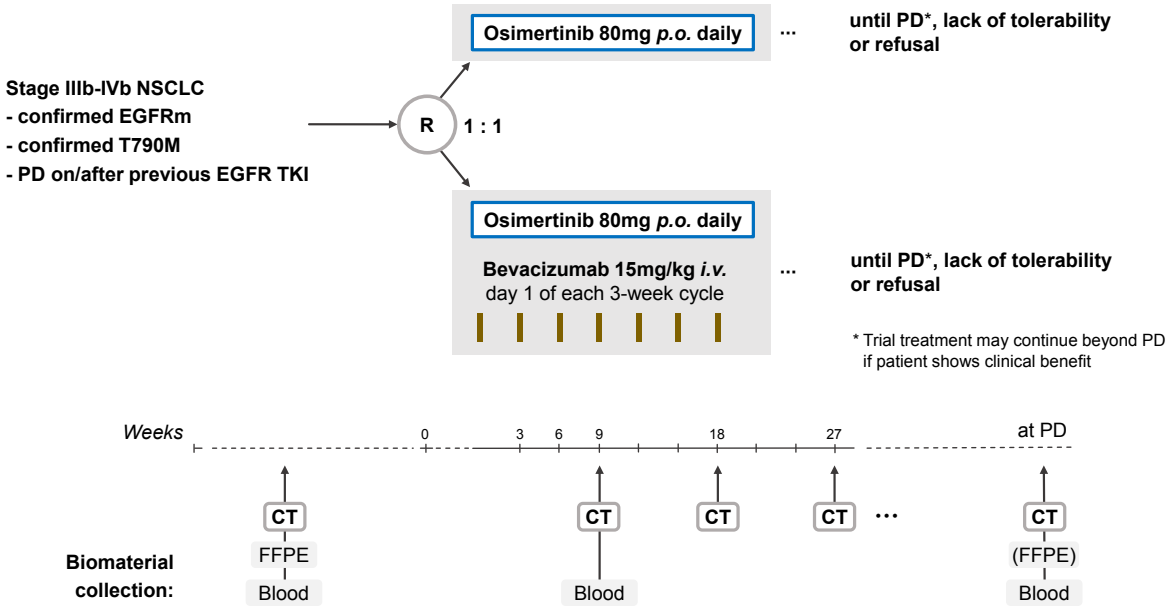
Please note: cytosmears are not sufficient for this trial.

15.2.2. Whole blood, serum and plasma samples

- 2.5 mL whole blood will be collected in PAXgene DNA tubes (for germline mutation assessment as a reference for tumour somatic mutation analysis) at baseline (after disease progression on the most recent treatment regimen).

- 2.5 mL whole blood will be collected in PAXgene RNA tubes at baseline (after disease progression on the most recent treatment regimen), 9 weeks after treatment start and at disease progression.
- Serum samples from 5 mL blood taken at baseline (after disease progression on the most recent treatment regimen), 9 weeks after treatment start and at disease progression, should be immediately frozen at -80ºC.
- Plasma samples from 5 mL blood taken at baseline (after disease progression on the most recent treatment regimen), 9 weeks after treatment start and at disease progression, should be immediately frozen at -80ºC.

It is anticipated that targeted NGS will be performed on DNA and RNA at a later time point. Whole genome squencing on tumour with blood as reference for germline DNA might also be a possibility. Nanostring expression analysis on blood and tumour could also be a priority at a later time point.



15.3. Biomaterial at disease progression on trial treatment

15.3.1. FFPE-material

- FFPE tumour block (preferred) or alternatively 10 tissue sections of 4 (-5) µm thickness, from re-biopsy at disease progression on trial treatment should be centrally submitted whenever feasible.

15.4. Submission of biomaterial

All biological samples collected during the conduct of the trial must be marked with the patient identifier issued by the EDC system and registered in the system. FFPE tumour tissue and blood samples to the central reference laboratory in Lausanne (Center for Experimental Therapeutics CTE, University of Lausanne, Switzerland).

15.4.1. Submission of FFPE material

- FFPE tumour material as defined in Section 15.2.1. and 15.3.1
- Pathology report from biopsy after disease progression on the most recent treatment regimen (all information allowing identification of the patient, e.g. patient name, day and month of birth, must be removed).
- Pathology report from re-biopsy at progression (all information allowing identification of the patient, e.g. patient name, day and month of birth, must be removed).

Tumour material should be submitted as soon as obtained (but not no later than 4 weeks after patient randomisation), and documented in the Biological Material Tracking eCRF in the database. On request, blocks can be returned to the submitting site within a reasonable time frame (est. 3 months) and after slides for the planned analyses have been cut.

All reports, slides, and blocks must be marked with the patient identification number issued by the EDC system. All information allowing identification of the patient should be removed or blackened.

Please ensure that the blocks and/or slides are carefully packaged according to the ***BOOSTER procedures manual***, as otherwise they could easily get damaged during transport.

Samples have to be sent to:
Center for Experimental Therapeutics CTE
University of Lausanne
(Exact address to follow)
CH-1011 Lausanne, Switzerland

Anonymised pathology reports should be uploaded via the EDC system. Please consult the ***BOOSTER procedures manual*** for specific instructions.

15.4.2. Submission of blood samples

For blood collection and serum preparation see ***BOOSTER procedures manual***.

Blood samples as defined in Sections 15.2.2.

Blood samples must be stored locally at -80ºC and will be kept at the participating site until shipment. Shipments will be arranged centrally once a site has collected all blood samples after the inclusion of the last patient. Samples have to be sent to the same address as indicated above.

16. Trial procedures

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

16.1. Safety assessments

16.1.1. Physical examination

Physical examination includes: PS, blood pressure, heart rate, temperature, body weight, height (only at baseline), general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

16.1.2. Resting 12-lead ECG

Patients should be monitored for ECG changes at every cycle. ECGs should be reviewed and any abnormalities noted.

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes. All ECGs should be recorded with the patient in the same physical position. For each time point three ECG recordings should be taken at 5 minute intervals. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the trial if possible.

The investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, ECG intervals and an overall evaluation will be recorded.

16.1.3. Left ventricular ejection fraction (LVEF)

Osimertinib and its active metabolite may also inhibit HER2. For this reason LVEF should be measured at baseline, then at least every 15 weeks (±1 week) from the time of first dose throughout the treatment period and when clinically indicated. It is up to the investigators choice to measure LVEF by either echocardiogram or MUGA scan. The same technique must be used within a patient.

16.1.4. Ophthalmologic exam

Full ophthalmic assessment, including slit lamp examination, should be performed at screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Ophthalmology examination results should be collected and documented in the eCRF.

Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings. These photographs should be available for submission to ETOP medical review if necessary.

16.2. Tumour assessment

Radiological tumour assessment by CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included) will be done as indicated in section 13.1 until PD.

16.3. Baseline evaluations before randomisation

The following examinations should be done within 28 day before randomisation. If examinations were done prior to 28 day before randomisation, they have to be repeated before treatment start.

Note: evaluations marked with * have to be repeated within 7 days prior to trial treatment start.

16.3.1. Written informed consent:
before any trial specific evaluations or interventions (within 6 weeks prior randomisation)

16.3.2. Medical history:
including baseline symptoms, smoking history, medications, comorbidities and allergies

16.3.3. *Physical examination:
Including PS, blood pressure, heart rate, temperature, body weight, height, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

16.3.4. Resting 12-Lead ECG

16.3.5. LVEF
Echocardiogram or MUGA scan should be measured at baseline.

16.3.6. *Pregnancy test
Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine beta-HCG pregnancy test within 7 days before randomisation.
Note: Test has to be repeated before treatment start, if treatment does not start within 72 hours of the previous test

16.3.7. *Chemistry
serum albumin, glucose, potassium, sodium, calcium, amylase, lipase and LDH

16.3.8. *Haematology
haemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count)

16.3.9. *Liver function test

total bilirubin, ALT, AST, ALP, GGT

16.3.10. *Renal function test
urea, uric acid, serum creatinine, creatinine clearance (Cockroft-Gault).

16.3.11. *Urine analysis (using dipstick)
pH, proteins, glucose, blood
specific gravity, elements and microscopic examination if needed.

16.3.12. Coagulation profile
international normalized ratio

16.3.13. Ophtalmologic exam
including slit lamp examination.

16.3.14. Radiological tumour assessment
by CT scan of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included), performed within 6 weeks before randomisation.

16.3.15. Confirmation of EGFRm
Histological or cytological confirmation of exon 19 deletion or exon 21 L858R mutation by a certified local laboratory.

16.3.16. Confirmation of T790M
Determined from biopsy (preferred) or on serum circulating tumour DNA by a certified local laboratory, that perform this within their routine practice. These samples must be taken after disease progression on the most recent EGFR TKI regimen.

16.3.17. Biological material
Tumour tissue and whole blood, serum and plasma samples after disease progression on the most recent treatment regimen must be available for central confirmation of T790M and further translational research studies. Submission of the same type of material as used for local identification of T790M is critical for central confirmatory analysis.

16.4. Evaluations in the experimental arm

At each treatment cycle

The following evaluations have to be done on day 1 of every treatment cycle (or within 3 days before these dates):

16.4.1. Recording of symptoms, adverse events and concomitant medications.

16.4.2. Physical examination:
Including PS, blood pressure, heart rate, temperature, body weight, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen,

lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

16.4.3. Resting 12-Lead ECG

Patients should be monitored for ECG changes at every cycle. ECGs should be reviewed and any abnormalities noted.

16.4.4. LVEF

Echocardiogram or MUGA scan should be measured at least every 15 weeks (±1 week) from the time of first dose of osimertinib throughout the treatment period and when clinically indicated. In the event of an absolute decrease of 10% from baseline and below 50%, withhold osimertinib for up to 4 weeks. If improved to baseline it can be restarted, but if not, then discontinue.

16.4.5. Chemistry

serum albumin, glucose, potassium, sodium, calcium, amylase, lipase and LDH

16.4.6. Haematology

haemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count)

16.4.7. Liver function test

total bilirubin, ALT, AST, ALP, GGT

16.4.8. Renal function test

urea, uric acid, serum creatinine, creatinine clearance (Cockroft-Gault).

16.4.9. Urine analysis (using dipstick)

pH, proteins, glucose, blood

specific gravity, elements and microscopic examination if needed.

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

In addition before bevacizumab cycle 4

Within 3 days prior to cycle 4:

16.4.10. Whole blood, serum and plasma samples

Blood samples for translational research have to be collected within 3 days prior to cycle 4.

16.5. Evaluations in the control arm

The following evaluations have to be done every 3 weeks (±3 days):

16.5.1. Recording of symptoms, adverse events and concomitant medications.

16.5.2. Physical examination:

Including PS, blood pressure, heart rate, temperature, body weight, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

16.5.3. Resting 12-Lead ECG

Patients should be monitored for ECG changes at every cycle. ECGs should be reviewed and any abnormalities noted.

16.5.4. LVEF

Echocardiogram or MUGA scan should be measured at least every 15 weeks (±1 week) from the time of first dose of osimertinib throughout the treatment period and when clinically indicated. In the event of an absolute decrease of 10% from baseline and below 50%, withhold osimertinib for up to 4 weeks. If improved to baseline it can be restarted, but if not, then discontinue.

16.5.5. Chemistry

serum albumin, glucose, potassium, sodium, calcium, amylase, lipase and LDH

16.5.6. Haematology

haemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count)

16.5.7. Liver function test

total bilirubin, ALT, AST, ALP, GGT

16.5.8. Renal function test

urea, uric acid, serum creatinine, creatinine clearance (Cockroft-Gault).

16.5.9. Urine analysis (using dipstick)

pH, proteins, glucose, blood

specific gravity, elements and microscopic examination if needed.

In addition at 9 weeks

The following additional evaluations have to be done 9 weeks (±1 week) after start of trial treatment:

16.5.10. Whole blood, serum and plasma samples

Blood samples for translational research have to be collected 9 weeks (±1 week) after trial treatment start.

16.6. Evaluations at disease progression

At progression, the following assessments are required:

16.6.1. Radiological tumour assessment
by CT scan of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included).

16.6.2. Biological material

- Tumour tissue from re-biopsy (strongly encouraged)
- Whole blood, serum and plasma (mandatory)

for further translational research studies.

16.7. Evaluation under treatment beyond progression

In case of clinical benefit, with physician and patient agreement, trial treatment can continue beyond confirmed progression for as long as the patient may still derive benefit as per investigator decision.The following evaluations have to be done on day 1 of every treatment cycle or every 3 weeks (or within 3 days before these dates)

16.7.1. Recording of symptoms, adverse events and concomitant medications.

16.7.2. Physical examination:
Including PS, blood pressure, heart rate, temperature, body weight, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

16.7.3. Resting 12-Lead ECG
Patients should be monitored for ECG changes at every cycle. ECGs should be reviewed and any abnormalities noted.

16.7.4. LVEF
Echocardiogram or MUGA scan should be measured at least every 15 weeks (±1 week) from the time of first dose of osimertinib throughout the treatment period and when clinically indicated. In the event of an absolute decrease of 10% from baseline and below 50%, withhold osimertinib for up to 4 weeks. If improved to baseline it can be restarted, but if not, then discontinue.

16.7.5. Chemistry
serum albumin, glucose, potassium, sodium, calcium, amylase, lipase and LDH

16.7.6. Haematology
haemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count)

16.7.7. Liver function test
total bilirubin, ALT, AST, ALP, GGT

16.7.8. Renal function test
urea, uric acid, serum creatinine, creatinine clearance (Cockroft-Gault).

16.7.9. Urin analysis
specific gravity, pH, glucose, blood using a dipstick; elements and microscopic examination if needed.

16.8. Evaluations at the end of treatment visit

Patients are considered to be on trial treatment for as long as they receive either osimertinib and/or bevacizumab. At the end of all trial treatment and irrespective of the reason for stopping treatment, an end of treatment visit at the centre is to be scheduled within 30 days following the decision to stop trial treatment or within 30 days after planned treatment start if treatment never started. This visit has to be done for all patients, including those who did not start trial treatment.

In case treatment was delayed due to AEs and could not be resumed, the end of treatment visit should be performed within 10 weeks after the last dose. The following procedures should be performed:

16.8.1. Recording of symptoms, adverse events and concomitant medications

16.8.2. Physical examination:
Including PS, blood pressure, heart rate, temperature, body weight, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

16.8.3. Resting 12-Lead ECG
ECGs should be reviewed and any abnormalities noted.

16.8.4. Chemistry
serum albumin, glucose, potassium, sodium, calcium, amylase, lipase and LDH

16.8.5. Haematology
haemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count)

16.8.6. Liver function test
total bilirubin, ALT, AST, ALP, GGT

16.8.7. Renal function test
urea, uric acid, serum creatinine, creatinine clearance (Cockroft-Gault).

16.8.8. Urin analysis
specific gravity, pH, glucose, blood using a dipstick; elements and microscopic examination if needed.

16.9. Evaluations in the follow-up phase (post treatment) before progression

Patients who discontinue trial treatment before progression should have the following examinations documented every 9 weeks (±1 week) starting from the end of treatment visit

until trial end (e.g. approximately 18 months after randomisation of the last patient). The following evaluations will be done:

16.9.1. Physical examination:
Including PS, blood pressure and body weight.

16.10. Evaluations in the follow-up phase beyond progression of disease

Patients with progression that ends trial treatment will be followed up every 12 weeks (±2 weeks) starting from date of progression until trial end (e.g. up to 2 years after the randomisation of the last patient). They should have documented:

16.10.1. Survival

16.10.2. Further lines of treatment

17. Case report forms and documentation

17.1. Case report forms schedule

eCRFs will only be available on-line at the electronic data capture (EDC) facility ETOPdata. No paper forms will be used, with the exception of a paper SAE form and pregnancy form in case of system unavailability.

Table 8: Case report forms:

eCRF in ETOPdata	**To be completed**
1 - Eligibility Check and Randomisation	Within 28 days of start of baseline evaluations
2 - Baseline	Within 14 days after randomisation
3 - Tumour Assessments	Baseline for randomisation: within 14 days after randomisation; During trial until tumour progression: within 14 days of date of each radiological imaging.
4 - Concomitant Medications	Continously from date of randomisation to 30 days after end of trial treatment; To be updated - within 14 days after randomisation - within 14 days of start of each Experimental Arm / Control Arm cycle - within 14 days of End of Treatment visit or within 14 days of Follow-up visits.

eCRF in ETOPdata	**To be completed**
5 - Experimental Arm / Control Arm	Within 14 days of start of each Experimental Arm cycle; Within 14 days of each Control Arm visit.
6 - Adverse Events	Continuously from date of Informed Consent signature to 30 days after all treatments discontinuation; To be updated - within 14 days of randomisation (baseline symptoms) - within 14 days of start of each Experimental Arm / Control Arm cycle - within 14 days after End of Treatment visit or within 14 days of Follow-up visits.
7 - Serious Adverse Event Initial Reports	Within 24h of awareness of SAE; Must be submitted via ETOPDdata, submission via fax to ETOP safety office only in case of unavailability of ETOPdata.
8 - Serious Adverse Event Follow-up Reports	Within 15 days of completion of initial report. If event was not resolved after 15 days, submit an additional report within 7 days of resolution of event.
9 - End of Treatment	Within 14 days after End of Treatment visit (which is to take place within 30 days following the decision to stop trial treatment).
10 - Follow-up	<u>Follow-up before progression:</u> Within 14 days of clinical follow-up visits (which will take place every 9 weeks (+/-1 week) until tumour progression); <u>Follow-up after progression:</u> Within 14 days of clinical follow-up visits (which will take place every 12 weeks (+/-2 weeks) from date of progression; <u>Follow-up on death:</u> Within 14 days upon awareness of death.
11 - Pregnancy	Within 24h of first documentation of pregnancy; Within 14 days of end of pregnancy.

eCRF in ETOPdata	To be completed
12 - Biological Material Tracking	This eCRF is to be completed incrementally. Entries are to be made: - within 4 weeks of randomisation: for information pertaining to “Tumour material at enrollment” (after disease progression on the most recent treatment); - immediately after local storage of blood samples (on same day): for information pertaining to “Date of blood draw”; - immediately (on same day) after submission of material (FFPE and blood) for central biobanking: for “Date Sent to Central Biobank”; - within 4 weeks of progression: for information pertaining to “Tumour material from re-biopsy at progression” (after trial treatment, optional).
13 - WC/LFU	Within 14 days of awareness of withdrawal of consent or loss to follow-up.

18. Statistical considerations

18.1. Primary objective

The primary objective of this randomised phase II trial is to assess the efficacy of the combination of osimertinib and bevacizumab versus osimertinib alone in terms of PFS, assessed by RECIST 1.1, for patients with locally advanced or metastatic (stage IIIb-IVb) EGFRm (exon 19 deletion or exon 21 L858R) NSCLC with T790M resistance mutation at progression on prior EGFR TKI therapy.

18.2. Sample size determination

The current randomised phase II trial is a superiority trial aiming to compare PFS between the two randomised arms (combination of osimertinib and bevacizumab versus osimertinib alone). An interim efficacy analysis for the primary endpoint (PFS) is also included.

Our target population includes patients with locally advanced or metastatic (stage IIIb-IVb) NSCLC with EGFR mutation (exon 19 deletion or exon 21 L858R) and T790M resistance mutation at progression on prior EGFR TKI therapy.

The median PFS for the target population under osimertinib alone is assumed to be 11 months [53].

Patient accrual is assumed to be non-linear with increasing rate to 6 per month, after the first 6 months.

In order to detect a 36% improvement in PFS under the combination of osimertinib and bevacizumab with 80% power at the 5% one-sided significance level, a total number of 126 events is required. For the targeted HR=0.64, corresponding to an increase for the median PFS from 11 to 17.2 months, a total of **154 randomized patients** need to be followed for an expected duration of 48 months, assuming an accrual period of 29 months. A cumulative loss to follow-up rate of 5% by 30 months is assumed.

Thus, in this phase II trial, **77 patients will be randomised 1:1 into each arm**. PFS is measured, according to RECIST v1.1, from randomisation and compared between treatment arms in the ITT cohort.

18.3. Trial duration

Total follow-up to observe the required events is expected to be 48 months. Taking into account a run-in period of 6 months and an additional 6 months for the final analysis report, the study duration is 5 years.

End of trial occurs when both of the following criteria have been satisfied:

- The trial is mature for the analysis of the primary endpoints as defined in the protocol
- The database has been fully cleaned and frozen for this analysis.

18.4. Analysis populations

18.4.1. Efficacy Cohort

The primary statistical analysis of the efficacy data will include all randomised subjects and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not receive trial treatment will be included in the ITT population.

18.4.2. Safety Cohort

The safety analysis population consists of all subjects who received at least one dose of trial treatment according to the treatment they actually received, regardless of their allocated treatment at randomisation.

18.5. Evaluation of primary and secondary objectives

Primary analysis on PFS will be performed overall and stratified by the randomisation stratification factors. An intent to treat primary efficacy analysis will be performed, including all randomised patients (= efficacy cohort).

PFS, OS as well as all time-to-event endpoints will be presented and evaluated from date of randomisation. The primary endpoint of PFS will be estimated by the Kaplan Meier method and compared between treatment groups. Similar analysis will be performed for OS and the other time-to-event time-points. Comparisons between the two treatment arms will be based on stratified logrank tests. In addition, stratified (by the randomisation stratification factors) and multivariate Cox models will be used for exploring the association of PFS (and the other time-to-event endpoints) with treatment in the presence of prognostic factors.

The two treatment groups will also be compared with respect to secondary efficacy and tolerability endpoints. No multiplicity adjustment will be performed for these analyses.

Clinical efficacy will be further described by objective response rate (ORR, defined as percentage of patients reaching a complete or partial response) based on RECIST 1.1 response criteria and disease control rate (DCR) along with 95% exact confidence intervals, overall and by treatment arm. ORR and DCR will be compared between the two treatment groups using Fisher's exact tests and Cochran-Mantel-Haenszel test stratified by the stratification factors of the trial (odds ratio will also be provided). Logistic regression models will be further applied to investigate the treatment effect, adjusting for stratification factors and variables of clinical interest. Duration of response and clinical benefit (including patients with at least stable disease as described in section 14.3) will also be compared between the two treatment groups, using Kaplan-Meier method.

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

The correlation of biological markers with PFS will be evaluated by univariate and multivariate Cox proportional hazards regression.

Statistical analysis for the primary, secondary endpoints and translational research will be described in detail in the Statistical Analysis Plan (SAP) document.

18.6. Early safety analysis

This phase II trial will evaluate the combination of osimertinib (80 mg, orally, once daily) with bevacizumab (15 mg/kg as *i.v.* infusion every 3 weeks). This allows a direct comparison for early safety signals. There will be a safety interim evaluation after the first 10 patients have been randomised to the experimental arm (total of 20 patients, 10 in the experimental and 10 in the control arm) and have received trial treatment for 30 days. This first safety evaluation will be submitted to the ETOP Independent Data Monitoring Committee (IDMC) for advice. The recruitment into the trial will continue while safety is evaluated.

Safety evaluations will be performed twice a year and submitted to the ETOP IDMC at their regular meeting.

18.7. Interim efficacy analysis

The interim efficacy analysis will be carried out when 63 (out of the 126) events are available. This is expected to occur approximately 26 months after the randomisation of the first patient.

According to O' Brien-Fleming approach, the treatment effect on PFS will be tested at type I error rate of 0.6%. If the boundary is crossed in favour of the alternative, the recruitment will stop early and a significant PFS benefit will be claimed for the combination.

19. Criteria for termination of the trial

19.1. General criteria for termination of the trial

The trial may be discontinued early in parts or completely if the information on the IMPs leads to doubt as to the benefit/risk ratio, by decision of ETOP Foundation Council upon recommendation of the ETOP 10-16 BOOSTER Steering Committee and IDMC. Specific considerations will be based on the interim safety and efficacy evaluations.

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

19.2. Discontinuation of protocol treatment for individual patients

Protocol treatment should be stopped in the following situations:

- Disease progression according to RECIST criteria 1.1, except if the patient may still derive benefit as per investigator decision.
- Occurrence of unacceptable toxicities. Stopping protocol treatment is determined by medical judgment of the treating physician.
- Patients experiencing corneal ulceration or ILD will not be permitted to restart trial treatment.
- Inter-current severe illnesses which would in the judgment of the investigator affect assessments of the clinical status to a significant degree and require discontinuation

of protocol therapy. **Note**: Diagnosis of another neoplastic disease (second malignant tumour) does not mandate a stop of trial therapy, patients may continue to receive protocol treatment after appearance of a second primary tumour, stopping protocol treatment is determined by the medical judgment of the treating physician.

- Request by the patient. Patients have the right to refuse further trial treatment at any time during the trial. Such patients will remain in the trial and will be transferred to the follow-up phase.
- If a patient refuses to have the treatments or follow-up examinations and tests needed to determine whether the treatment is safe and effective.

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

19.3. Withdrawal of consent

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

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

20. Ethics aspects, regulatory approval, and patient informed consent

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

20.1. Ethical Review Board/Ethics Committee

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

The Ethical Review Board/Institutional Review Board (ERB/IRB) written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent. Documentation of Ethics Committee approval must be sent to the ETOP coordinating office prior to randomisation of the first patient.

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

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

20.2. Regulatory approval procedures

If applicable, in addition to the approval of the ethics committee according to national legislation, the protocol, protocol related documents including patient information and informed consent and other documents as required locally must be submitted to and be approved by the health authority. Documentation of health authority approval must be sent to the ETOP coordinating office prior to participating centre activation.

20.3. Informed consent

Informed consent for each patient will be obtained prior to initiating any trial procedures in accordance with the "patient information and informed consent" (see Appendix 1). One signed and dated, a copy of the informed consent must be given to each patient and the original copy must be retained in the investigator's trial records. The informed consent form must be available in the case of data audits. Verification of signed informed consent and the date signed are required for randomisation into this trial.

The "Declaration of Helsinki" recommends that consent be obtained from each potential patient in biomedical research trials after the aims, methods, anticipated benefits, and

potential hazards of the trial, and discomfort it may entail, are explained to the individual by the physician. The potential patient should also be informed of her/his right to not participate or to withdraw from the trial at any time. The patient should be told that material from her/his tumour and blood and serum samples will be stored and potentially used for additional studies not described in this protocol.

If the patient is in a dependent relationship to the physician or gives consent under duress, the informed consent should be obtained by an independent physician. If the patient is legally incompetent (i.e. a minor, or mentally incompetent), informed consent must be obtained from the parent, legal guardian, or legal representative in accordance with the law of the country in which the trial is to take place. By signing this protocol, the investigator agrees to conduct the trial in accordance with GCP and the "Declaration of Helsinki".

ETOP recognises that each institution has its own local, national, and international guidelines to follow with regard to informed consent. Therefore, we provide a template information sheet and informed consent form (appendix 1), which can be edited to incorporate information specific to your institution. The template patient information sheet and informed consent has been written according to ICH guidelines which state the informed consent should adhere to GCP and to the ethical principles that have origin in the "Declaration of Helsinki". The final version should receive the IRB / local EC approval in advance of its use. Centres should send their locally modified PIS/IC to ETOP for review and approval before submitting to their ethics committee.

21. Governance and administrative issues

21.1. Final report

A final clinical trial report will be written and distributed to health authorities as required by applicable regulatory requirements

21.2. Steering Committee

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

21.3. Independent Data Monitoring Committee

The ETOP IDMC is a standing committee of independent experts. Its role is the systematic review of the accumulating data from all ongoing ETOP sponsored trials including accrual, safety and efficacy. The primary mandate of the IDMC is to safegueard the interest and safety of the patients in the trial and to ensure the scientific integrity of the trial. Details of the particular responsibilities and procedures within the ETOP 10-16 BOOSTER trial are summarised in the ETOP IDMC Guidelines and the trial-specific IDMC charter.

The trial will be presented for review to the ETOP IDMC at each of their bi-annual meetings. Based on this review, the IDMC recommends to the trial Steering Committee whether to continue, modify or stop the trial.

21.4. Publication

The results of the trial will be published according to the ETOP publication guidelines (appendix 2).

21.5. Clinical trial insurance

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

21.6. Quality assurance

ETOP conducts trials according to the ICH GCP guidelines. The Trial data manager reviews each eCRF as it is received. In addition, the ETOP medical reviewer reviews each case at specific time points. ETOP conducts periodic audit visits to ensure proper trial conduct, verify compliance with GCP, and perform source data verification.

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

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

21.7. Protocol adherence

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

21.8. Data protection

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

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

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

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

21.9. Record retention

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

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

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

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