Clinical study protocol

A phase IIa clinical trial to evaluate the safety and efficacy of osimertinib (AZD9291) as first-line treatment in patients with locally advanced or metastatic EGFR-mutant non-small cell lung cancer and concomitant EGFR T790M mutation at time of diagnosis (AZENT study)

Code: MedOPP112

Study drug:	Osimertinib (AZD9291)
EudraCT No.:	2015-004828-66
ESR code:	ESR-15-10768
ClinicalTrials.gov No.:	NCT02841579
Protocol No.:	MedOPP112
Protocol date:	May 21, 2018

Protocol review history	
Initial approved version:	v 2 June 22, 2016
Amendment No. 1	v 3 May 21, 2018
Amendment No. 2:	
Amendment No. 3:	

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary objective

To evaluate the efficacy of osimertinib (AZD9291), in terms of the objective response rate (ORR) in patients with advanced non-squamous NSCLC with EGFR mutations and the EGFR T790M mutation at diagnosis, according to RECIST 1.1 criteria.

Primary endpoint: Objective Response Rate (ORR) which is defined as the Complete Responses [CR] or Partial Responses [PR] to treatment in accordance with the guidelines of RECIST version 1.1 criteria. An objective response should be confirmed at least 4-6 weeks after the initial response.

2.2 Secondary objectives

- To determine the safety and tolerability profile of osimertinib (AZD9291), measured using the number and severity of AEs entered into the Case Report Form (CRF); chemistry, blood count, vital signs, physical examination, weight, ECG and performance status (ECOG).
- To determine secondary efficacy parameters such as the progression-free survival (PFS), overall survival (OS), time to treatment failure (TTF), duration of response (DOR), disease control rate (DCR) and tumor shrinkage (TS).
- To correlate the parameters of clinical response efficacy documented with the EGFR mutational status.
- To carry out a longitudinal analysis of EGFR mutations (including the T790M mutation) in plasma and serum.
- To determine levels of BIM mRNA as well as mRNA levels of other biomarkers related to EGFR TKI response and determine whether they are predictors of treatment response.
- To identify mechanisms of acquired resistance to osimertinib (AZD9291); mutations at the site of covalent binding to the drug (C797) or other mutations in tissue or blood.
- To analyze biomarkers related to mechanisms of resistance to the treatment.

Secondary efficacy endpoints: Patient safety and adverse events will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE) of the U.S. National Cancer Institute (NCI), version 4. Grade 3 or 4 adverse events and serious adverse events will be assessed to determine the safety and tolerability of the various combinations of drugs.

Secondary efficacy endpoints:

- The progression-free survival (PFS) is defined as the time from the start of the treatment to death or disease progression, assessed by the investigator in accordance with RECIST v1.1, regardless of whether the patient has discontinued the study treatment or is receiving treatment with another drug.
- Overall survival (OS) is defined as the time from the start of treatment to the time of death due to any cause.
- Time to treatment failure (TTF) is defined as the time from the start of treatment to the time at which the patient discontinues treatment due to any cause, including disease progression assessed by the investigator in accordance with RECIST v1.1, toxicity, death or at the patient's request.
- Duration of response (DOR) is defined as the time from the first documented response to documented disease progression or death, in accordance with RECIST 1.1 criteria.

- Disease control rate (DCR) is defined as the percentage of patients with CR, PR or stable disease for a minimum of 24 weeks, assessed in accordance with the modified Response Evaluation Criteria in Solid Tumors (RECIST v. 1.1), version 1.1.
- Tumor shrinkage (TS) is defined as the percentage of tumor shrinkage from baseline (obtained from the sum of the largest diameters of the target lesions) according to RECIST v1.1 criteria.

Molecular secondary endpoints

- Correlation ratio of mutational status and documented clinical response.
- A progress curve showing the EGFR mutational status (including the T790M mutation) in plasma and serum longitudinally.
- Percentage levels of BIM mRNA as well as mRNA levels of other biomarkers related to EGFR TKI response.
- Percentage of patients with mutations at the site of covalent binding to the drug (C797) or other mutations in tissue and correlation ratio of documented clinical response.

3 STUDY OVERVIEW

3.1 Type of study

This is a multicenter, open-label, non-controlled phase IIa clinical trial.

3.2 Study design

The design of this study is divided into three well-defined phases:

- **Screening phase**

During this phase, subject eligibility is determined, including the genotyping of the tumor and documentation of baseline characteristics. Considering that the study requires a sample of 73 patients with metastatic NSCLC (preferably women, with adenocarcinoma, former smokers or never-smokers) with activating EGFR mutations and concomitant T790M mutation, and bearing in mind that the estimated frequency of the concomitant T790M mutation in patients with metastatic NSCLC with activating EGFR mutations is 50% based on the frequency found in previous studies (Costa et al. 2010; Chen et al. 2016; Stahel RA, Dafni U, Gautschi O, et al. September 25-29; Costa et al. 2014), we estimate that it will be necessary to screen 146 patients with EGRF mutation to identify 73 patients with EGFR mutation and concomitant T790M mutation. This phase of the study will begin once the informed consent is signed by the patient, and the procedures to be performed are described in section 5 of the protocol.

- **Treatment phase:**

When a patient harboring both mutations is identified and the study screening criteria have been met, the patient will receive **a dose of osimertinib (AZD9291) 80 mg every 24 hours, in tablets for oral administration.** The study treatment will continue until one of the following situations arises:

- Disease progression is confirmed radiologically and unequivocally, except for new metastases in CNS or isolated progression of previously treated lesions in the CNS. Patients who present disease control outside of CNS, defined as confirmed PR or CR of any duration, or SD lasting ≥3 months, but who have developed metastases in CNS that can be treated with radiation therapy, will be allowed to continue receiving study treatment until they experience systemic progression of the disease outside CNS and/or additional progression in the CNS that cannot be treated with additional radiation

therapy.

- Adverse event(s) which, according to the protocol or in the opinion of the investigator, can cause serious or permanent damage or which rule out further treatment with the study drug.
- General or specific changes in the patient's health state which, in the opinion of the investigator, make further treatment unacceptable.
- Major protocol non-compliance.
- Patient's withdrawal from the study.
- Death.
- Until the end of study, after a maximum of 78 weeks from the administration of the first dose of treatment by the last enrolled patient (see Section 3.7).
- Study is canceled by the sponsor.

In the event a dose change is required during the treatment, 40 mg tablets can be administered as described in section 6.9.

Treatment with osimertinib (AZD9291) is continuous, and every 21-day period will be considered one cycle. The treatment will begin on day 1 of the first cycle.

Follow-up visits will take place every 6 weeks to obtain basic safety data and every 12 weeks to obtain complete efficacy and safety data.

At the end of the study, patients may continue taking commercial osimertinib (TAGRISSO™) if it provides benefits in the investigator's opinion.

- **Follow-up phase:**

Once the treatment phase is completed, a biopsy should be performed to identify acquired mechanisms of resistance to the drug and the follow-up phase will begin. The frequency of clinical assessments during this phase of the study will not differ from that performed in the course of standard clinical practice. Follow-up visits will take place every 12 weeks; information on the patient's health state will be included in the CRF, as well as any treatment received until the end of study.

3.5 Duration of study treatment (treatment phase)

The study treatment period is defined as the time elapsed between the first and the last dose of drug taken.

The study treatment should be discontinued if at least one of the reasons described in Section 3.2 occur, and the reason(s) for discontinuation will be recorded in the patient's history and in the corresponding case report form.

3.6 Duration of post-treatment follow-up period (follow-up phase)

The follow-up period is defined as the time elapsed from the last dose of treatment received and death, withdrawal of consent or end of study (EoS), whichever occurs first.

3.7 End of study (EoS)

The EoS is defined as the Last Patient Last Visit (LPLV) at the end of the follow-up period. This is the last time point for data collection. It can be a clinical visit or a laboratory sample. The EoS will take place in a maximum of 78 weeks after the first dose administered to the last patient enrolled in the study.

However, the interim analysis will assess the primary objective and all the safety and efficacy objectives limited to a window of up to 42 weeks. After database lock at 42 weeks, patients will continue to be treated and controlled until the end of study date (see Section 8.6 Interim analysis).

4 PATIENT SCREENING

The following eligibility criteria can be used in the screening of patients for whom the protocol treatment is deemed suitable. In order to determine whether this protocol is suitable for a given patient, all medical and non-medical criteria should be taken into consideration.

4.1 Study Population

Patients diagnosed with stage EIIIB or IV non-small cell lung cancer harboring the EGFR activating mutation and concomitant T790M mutation who have not received prior treatment for this advanced disease will be enrolled in this study. Patients are not eligible if they are candidates for local curative treatment.

The analysis of EGFR mutational status (del19, L858R, L861Q or G719X) may be previously performed at each of the participating sites, but the tumor material taken from all patients should be submitted to the central laboratory for supportive analysis and T790M mutation analysis.

The patient's signed informed consent should be obtained before sending the tumor tissue sample to the central laboratory.

4.2 Inclusion criteria

Patient eligibility will be reviewed and documented by a suitable member of the investigator's study team before the patients are enrolled in the study.

Patients must meet all the following inclusion criteria to be enrolled in the study:

1. Patient aged 18 years or older.
2. Patients with histological confirmation of metastatic, non-squamous or locally advanced non-small cell lung cancer (NSCLC) who are not candidates for local curative treatment, with an activating EGFR mutation and concomitant T790M mutation.
3. Patients with an M1a stage according to the TNM version 7 including M1a (malignant effusion) or M1b (distant metastasis), or locally advanced disease that is not a candidate for

curative treatment (including patients who progress after chemoradiotherapy in stage III disease).

4. Patients with an EGFR deletion or mutation in exon 19, exon 21 (L858R, L861Q) or exon 18 (G719X) and concomitant T790M mutation before treatment confirmed centrally.
5. ECOG (Eastern Cooperative Oncology Group) performance status less than or equal to 2.
6. Existence of measurable or evaluable disease (according to RECIST 1.1 criteria). Patients with asymptomatic and stable brain metastases are eligible for the study.
7. Possibility of obtaining sufficient tissue sample, via a biopsy or surgical resection of the primary tumor or metastatic tumor tissue, if no systemic treatment has been performed for advanced or metastatic disease from sample collection to enrollment in the trial.
8. Life expectancy ≥12 weeks.
9. Adequate hematologic function: Absolute neutrophil count (ANC) >1.5 x 109/L, platelet count >100.0 x109/L and hemoglobin >9.0 g/dL (>6.2 mmol/L).
10. Appropriate coagulation (INR ≤1.5).
11. Adequate liver function: Total bilirubin <1.5 × ULN, ALT and/or AST <2.5 × ULN, alkaline phosphatase <5 ULN, except in the presence of single bone metastases and in absence of any liver disorders.
12. Adequate renal function: Calculated creatinine clearance >50 mL/min (Cockcroft-Gault) and proteinuria <2+ (dipstick).
13. Capacity to swallow, patient capable of completing treatment and accessible, ensuring proper follow-up.
14. Patients able to complete study and within geographical proximity allowing for adequate follow-up.
15. Resolution of all acute toxic effects of previous anti-cancer therapy (which can only be adjuvant or neoadjuvant) or surgical interventions not exceeding grade 1 according to the NCI CTCAE version 4.0 (except for alopecia or other side effects that the investigator does not consider to be a risk to patient safety).
16. All men or women of childbearing potential must use a contraception method during the study treatment and for at least 12 months after the last dose of the study drug. Sexually active men and women of childbearing potential who are unwilling to use a contraception method are not eligible for the study.
17. The written informed consent (IC) must be signed and dated by the patient and the investigator before any study intervention takes place.

4.3 Exclusion criteria

Any patient meeting **ANY** of the following criteria will be excluded from the study:

1. Locally advanced lung cancer candidate for curative treatment through radical surgery and/or radio(chemo)therapy.
2. Patients diagnosed with another lung cancer subtype, patients with mixed NSCLC with predominantly squamous cell cancer, or with any small-cell lung cancer component .
3. Patients with an EGFR deletion or mutation in exon 19, exon 21 (L858R, L861Q) or exon 18 (G719X) and T790M mutation before treatment that have not been confirmed centrally.

4. Patients who have received prior antineoplastic treatment for advanced disease.
5. Second active neoplasia; e.g., patients diagnosed with a potentially lethal cancer for which they may be receiving treatment (but are not obliged to do so).
6. Patients with just one measurable or evaluable tumor lesion that has been resected or irradiated prior to their enrollment in the study.
7. Medical history of Interstitial Lung Disease (ILD) induced by drugs, radiation pneumonitis requiring steroid treatment or any evidence of clinically active ILD.
8. Any of the following criteria:
   - Corrected QT Interval (QTc) >470 ms, obtained from ECG at rest, using the QTc value determined according to the clinical screening ECG machine.
   - Any clinically significant abnormality in ECG rhythm, conduction or morphology at rest.
   - Any factor that increases the risk of QTc prolongation or risk of irregular heartbeat or sudden inexplicable death under the age of 40 in first-degree relatives or any concomitant medications that prolong the QT interval.
9. Uncontrolled, active or symptomatic metastases of CNS, carcinomatous meningitis or leptomeningeal disease indicated by known clinical symptoms, cerebral edema and/or progressive neoplasia. Patients with history of CNS metastasis or compression of the spinal cord are eligible if they have received local final treatment (e.g., radiotherapy, stereotactic surgery) and if they have remained clinically stable without using anticonvulsants and corticosteroids for a minimum of 4 weeks prior to the first day of study treatment.
10. Refractory nauseas and vomiting, chronic gastrointestinal disease, inability to swallow study drug or significant intestinal resection that restricts the adequate absorption of osimertinib (AZD9291).
11. Patients who have had a surgical procedure unrelated to the study within 7 days prior to the administration of the drug or a significant traumatic lesion during the 4 weeks prior to starting the administration of the study drug, patients who have not recovered from the side effects of any major surgery or patients who might need major surgery during the course of the study.
12. Pregnant or breastfeeding women. Women of childbearing potential, including women who had their last menstrual period within the last two years, must have a negative serum or urine pregnancy test in the 7 days prior to the start of the treatment.
13. Patients who are not willing to use an adequate contraception method until 12 months after the last dose of study treatment.
14. Patients with a serious concomitant systemic disorder (e.g., active infection, including the HIV or heart disease) incompatible with the study (in the investigator's judgment) and previous history of bleeding diathesis.
15. Inability to swallow tablets.
16. Patients with a history of cancer that has been completely treated, with no evidence of malignant disease currently cannot be enrolled in the study if their radiotherapy and/or chemotherapy was completed less than 6 months prior and/or have received a bone marrow transplant less than 2 years before the first day of study treatment.
17. Prior treatment with cytotoxic radiotherapy and/or chemotherapy for advanced NSCLC; neoadjuvant/adjuvant radiotherapy and/or chemotherapy is permitted if at least 6 months have elapsed between the end of radiotherapy and/or chemotherapy and the first day of study treatment.

18. Patients who have received prior EGFR treatments for lung cancer.
19. Patients who have received treatment with an investigational drug within 3 weeks before their enrollment in the study.
20. Treatment with prohibited drugs within 14 days before the first day of study treatment.
21. Any other reason that the investigator deems to be incompatible with the patient's participation in the study.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Screening phase: Patient enrollment procedures

Study-specific assessments performed during the screening phase: Day 0 (patient enrollment pending re-confirmation of EGFR and confirmation of T790M in the central laboratory), Day 14 maximum (to confirm T790M during days 1-14) and Day 28 (to confirm remaining screening criteria during Days 15-42 after Day 0 of the screening phase).

Written informed consent from the patient must be signed before performing any study procedure.

By giving their consent, patients will be informed as to the nature of the study drug and will receive pertinent information regarding the study objectives, possible benefits and potential adverse events. They will also receive information on the follow-up procedures and possible risks they will be exposed to. This document also informs patients about how biological samples will be obtained and collected and its legal implications. After receiving the document, the patient will read it (or receive information verbally before witnesses) and will sign the previously approved informed consent. The patient will receive a signed copy of the informed consent. The patient can withdraw their consent and discontinue the study; this will not affect any future medical treatment.

Once this consent is obtained and upon confirmation that the patient meets the remaining screening criteria (through the available data in the medical history or by performing the corresponding necessary tests), the investigator staff will submit the tumor tissue samples (accompanied by the anatomy-pathology report) and serum/plasma to the central reference laboratory immediately for central evaluation of activating EGFR mutations and T790M mutation in exon 20. The characteristics and packaging of biological sample shipments are described in "Appendix 4: Instructions for shipment of biological samples to the central laboratory" of this protocol.

Within 7 working days, the central reference laboratory will inform as to whether there is sufficient material that is suitable for EGFR analysis and determination of T790M mutation.

A. If tissue quality and/or quantity is deemed unacceptable by the central reference laboratory, the study staff will be suitably informed and if a sample of tumor tissue cannot be obtained under better conditions, the patient will not be eligible for the study.

B. If the EGFR mutation and concomitant T790M status are not confirmed, the patient will not be eligible for the study. The central reference laboratory will inform the study staff as to the results of the analyses, which will be kept on file in the study documentation file of the participating site.

C. If the EGFR mutation and concomitant T790M status are confirmed, the results of the analyses will be sent to the investigator staff, who will then proceed to confirm the remaining patient screening criteria and proceed to enroll the patient in the study.

EGFR results of the test carried out in the local laboratory should be obtained up to 28 days prior to the patient's enrollment in the study.

At enrollment:

1. The sponsor will request the patient's demographic and clinical data related to screening criteria.

2. Each patient will be given a **Unique Patient Number (UPN)** for this study, provided by the sponsor. All data will be recorded in the appropriate CRFs using this identification number. This number will be provided to the central laboratory to ensure traceability of study samples.

Confirmation of patient's eligibility for study participation will be recorded in the Case Report Form (CRF). The investigator is responsible for safeguarding patient information (e.g., age, name, address, telephone number, social security number and study identification number), ensuring access to said information by health authorities if necessary. These records will remain confidential for the period of time stipulated by current legislation.

The screening period will include:

- Anamnesis and symptom assessment.
- Physical examination and measurement of weight, vital signs and performance status.
- Basic blood test that includes blood count (hemoglobin, hematocrit, RBC count, platelet count and leukocyte count with differential blood count [neutrophils, lymphocytes, monocytes, eosinophils and basophils]) and blood chemistry (sodium, potassium, calcium, chloride, magnesium, uric acid, total proteins, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase and total bilirubin) with renal function analysis (serum creatinine and creatinine clearance according to the Cockcroft-Gault formula), liver function (AST, ALT, ALP and bilirubin), glucose and coagulation (INR).
- Urine dipstick test for analysis of proteinuria.
- Pregnancy test, when applicable.
- 12-lead electrocardiogram.
- Tissue sample, which is then sent to central laboratory.
- Blood sample for the translational study, which is then sent to central laboratory.
- Antineoplastic therapy (if applicable).
- Assessment of concomitant medication (as specified in Section 3.3).
- CT, PET-CT and MRI of at least the chest and abdomen prior to starting the first cycle. Radiological study with CT, PET-CT or MRI that include at least the chest and abdomen.

5.2 *Treatment phase: Assessments*

The results of the reference tests or examinations performed prior to obtaining the informed consent and in the 28 days prior to treatment start may be used; it will not be necessary to repeat these tests for the screening.

All screening assessments should be performed and reviewed to confirm that the patients meet all the eligibility criteria prior to treatment start (Day 1). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Visits are organized in programmed cycles of 21 days (if there are no delays in treatment owing to the occurrence of a side effect). Dose reductions or delays are permitted, as described in section 6.9. All visits must occur within ± 3 working days from the scheduled date, unless otherwise stated in the schedule of assessments. All evaluations will be performed on the specific visit day unless a time frame is specified. Assessments scheduled on the day of study treatment administration should be performed prior to study treatment administration unless otherwise indicated. If a mandatory procedure described in the protocol falls on a bank holiday and/or weekend, this procedure should be performed on the day before or after the holiday (i.e. within a period of ± 3 working days), unless otherwise indicated.

Local laboratory assessments scheduled for Day 1 (prior to treatment) every two cycles should be performed within 72 hours prior in order to confirm if the treatment may continue (in each treatment visit scheduled every 2 cycles). The results of local blood tests should be reviewed, and this review will be recorded before administration of the study treatment.

Specific study assessments during treatment phase: Day 14 of

the first treatment cycle:

- Serum/blood draw for translational analysis.

During basic safety visits - Day 1 of each cycle every 2 cycles (every 6 weeks).

- Symptom assessment.
- Physical examination and measurement of weight, vital signs and ECOG performance status.
- Basic blood test that includes blood count (hemoglobin, hematocrit, RBC count, platelet count and leukocyte count with differential blood count [neutrophils, lymphocytes, monocytes, eosinophils and basophils]) and blood chemistry (sodium, potassium, calcium, chloride, magnesium, uric acid, total proteins, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase and total bilirubin) with renal function analysis (serum creatinine and creatinine clearance according to the Cockcroft-Gault formula), liver function (AST, ALT, ALP and bilirubin), glucose and coagulation (INR).
- Urine dipstick test for analysis of proteinuria.
- Antineoplastic therapy.
- Assessment of concomitant medications.
- Assessment of adverse events.
- Survival.

During full visits - Day 1 of each cycle every 4 cycles (every 12 weeks):

- Anamnesis and symptom assessment.
- Physical examination and measurement of weight, vital signs and ECOG performance status.
- Basic blood test that includes blood count (hemoglobin, hematocrit, RBC count, platelet count and leukocyte count with differential blood count [neutrophils, lymphocytes, monocytes, eosinophils and basophils]) and blood chemistry (sodium, potassium, calcium, chloride, magnesium, uric acid, total proteins, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase and total bilirubin) with renal function analysis (serum creatinine and creatinine clearance according to the Cockcroft-Gault formula), liver function (AST, ALT, ALP and bilirubin), glucose and coagulation (INR).
- Urine dipstick test for analysis of proteinuria.
- 3 12-lead electrocardiograms.

- Antineoplastic therapy.
- Assessment of concomitant medications.
- Assessment of adverse events.
- Tumor evaluation: CT, PET-CT and MRI of at least the chest and abdomen prior to starting the cycle every 4 cycles and every 12 weeks until the end of the treatment phase (Section 3.2).
- Survival.

Tissue and serum/plasma assessment for translational study:

- Tumor re-biopsy will be considered at the time of progression (as recommendation only) for analysis of possible mechanisms of resistance and future translational research at the reference laboratory.
- Blood/plasma collection prior to starting the cycle every 4 cycles and every 12 weeks until the end of the treatment phase (Section 3.2).

Biological sampling: Given that very little is known on how cancer develops resistance to pyrimidine-based EGFR inhibitors, mutations in tumor tissue or blood will be identified at the site of covalent binding to osimertinib (AZD9291) (C797) in addition to other mutations that can mediate resistance .
The first tissue samples should be taken before starting study treatment (see Appendix 6 for more details on tissue sampling procedures). Tumor re-biopsy will be considered at the time of progression (as recommendation only) for analysis of possible mechanisms of resistance and future translational research at the reference laboratory.
The first blood samples for serum and collection of plasma should be taken before starting study treatment (see Appendix 6 for more details on blood sampling procedures). The following samples should be taken at 2 weeks, and every 12 weeks thereafter (coinciding with assessments of responses using radiographic imaging) and at the time of progression.
At the time of site activation, the sponsor will provide cryovials and cryoboxes for the storage and transport of samples, as well as labels. This material will be provided by the central laboratory. No other cryovials or labels should be used for this study. If more tubes and labels are required, these should be requested from the sponsor in writing at least 3 weeks before they are required (see Appendix 6).

Anamnesis and demographic data: Anamnesis includes clinically significant diseases, surgical interventions, history of cancer (including prior antineoplastic treatments and procedures), history of smoking, alcoholism, drug addiction, as well as any medications (e.g., prescribed drugs, over-the-counter drugs, medicinal plants, homeopathic remedies, or food supplements) used by the patient in the 21 days prior to screening visit. Demographic data will include age, gender and race/ethnicity reported by the patient himself/herself.

Vital signs: These will include the measurement of height (only during screening), weight, respiratory rate, heart rate, blood pressure, and body temperature. Abnormal or significant changes in vital signs from baseline should be recorded as adverse events, if appropriate.

Physical examination: A complete physical examination should include an examination of head, eyes, ears, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, digestive, genitourinary and neurological systems. Changes to abnormalities identified during the baseline period should be recorded at all subsequent physical exams. New or worsening abnormalities should be recorded as adverse events, if applicable.

Physical exams should also include, as part of tumor assessment, evaluation of presence and degree of increase of lymph nodes, hepatomegaly and splenomegaly. Limited physical exams will focus on symptoms.

Response and tumor assessments: Tumor response will be assessed for all patients, unless they withdraw from the study for any reason not attributable to disease progression confirmed radiologically or clinically and who have not received an acceptable complete assessment of the disease. The measurable and non-measurable disease should be documented at screening and be re-assessed at every tumor assessment thereafter. The initial assessment of tumor response will be performed at the end of cycle 4. Thereafter, an efficacy follow-up will be carried out for all patients every 12 weeks during the study period, until disease progression, death, treatment discontinuation or study completion. In this study, response and disease progression will be assessed using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) (Appendix 2: Response Evaluation Criteria in Solid Tumors Guidelines (RECIST criteria) (version 1.1)).

A PET-CT, CT or MRI of at least the chest and abdomen should be performed at screening. If a positron emission tomography (PET)/CT is used in tumor assessments, the CT portion of the PET/CT should meet diagnostic quality requirements. Tumor assessments should include an assessment of all known and/or suspected sites of the disease wherever possible. Patients should have a series of selected lesions that can be assessed at each tumor assessment.

The same radiographic procedure employed at screening should be used throughout the study (e.g., the use of the same contrast protocol for CTs) The initial assessment of tumor response will be performed at the end of cycle 4. Thereafter, tumor response should be assessed every 12 weeks until disease progression or the end of the study (see definition in section 3.7). Response assessments will be evaluated by the investigator, using physical examinations, PET-CTs, CTs or MRI of at least the chest and abdomen, based on RECIST v criteria. 1.1 (Appendix 2: Response Evaluation Criteria in Solid Tumors Guidelines (RECIST criteria) (version 1.1)). In the case of patients who continue with study treatment after isolated brain progression, the frequency of radiological tests will be left up to the discretion of the investigator. PET-CT, CT and MRI scans may be obtained at any time when clinically indicated or if disease progression is suspected.

Radiographic assessments should always be performed in place of clinical examinations, unless lesions being monitored cannot be captured using imaging techniques, unless they are evaluable via clinical examination. According to the RECIST 1.1 criteria, imaging should be performed in color, and include a ruler to calculate lesion size.

Laboratory assessments

Laboratory tests will be performed in accordance with local standard treatment and clinical indications before treatment administration. These values should include: Hemoglobin, hematocrit, RBC count, platelet count and leukocyte count with differential blood count (neutrophils, lymphocytes, monocytes, eosinophils and basophils), sodium, potassium, calcium, chloride, magnesium, uric acid, total proteins, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, total bilirubin, creatinine, blood glucose level, coagulation and proteinuria.

Electrocardiograms: A 12-lead ECG will be performed at baseline, printed and kept on file along

with the patient's history. Thereafter, 3 electrocardiograms will be performed every 12 weeks until disease progression, death, treatment discontinuation or study completion. The QT interval should be recorded according to Fridericia's formula (QTcF).

ECOG performance status: Performance status will be determined using the ECOG performance status scale. Wherever possible, the patient's performance status should always be assessed by the same personnel throughout the study.

Grade	Scale
0	Fully active, able to carry on all pre-disease performance without restriction.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50 % of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Adverse events and toxicity to treatment: Safety and tolerability of all patients will be closely monitored throughout study treatment and the follow-up period. Patients will be assessed in order to detect any side effects before administering new bottles of the study treatment. New bottles of treatment will only be administered if clinical evaluation and local laboratory test results are acceptable.

5.3 Follow-up phase

Patients will be followed up until the patient dies or the study ends, whichever occurs first. The follow up of all patients will be performed until the last patient completes 78 weeks of treatment, progresses or dies, whichever occurs first.

At these follow-up contacts, information will be obtained on survival status and post-study antineoplastic therapy assessment. Contact by telephone is permitted.

Any events grade ≥2 will be followed until improvement to baseline levels is observed, complete recovery or resolution to grade 1, consent is withdrawn by the patient, patient death or until follow-up is no longer possible.

- Assessment schedule after progression or study discontinuation for any reason: After progression or study discontinuation for any reason, the following assessments will be performed within a maximum period of 28 days:
    - Anamnesis and symptom assessment.
    - Physical examination and measurement of weight, vital signs and ECOG performance status.
    - Basic blood test that includes blood count (hemoglobin, hematocrit, RBC count, platelet count and leukocyte count with differential blood count [neutrophils, lymphocytes, monocytes, eosinophils and basophils]) and blood chemistry (sodium, potassium, calcium, chloride, magnesium, uric acid, total proteins, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase and total bilirubin) with renal function analysis (serum creatinine and creatinine clearance according to the Cockcroft-Gault formula), liver function (AST, ALT, ALP and bilirubin), glucose and coagulation (INR).
    - Urine dipstick test for analysis of proteinuria.
    - 12-lead electrocardiogram.
    - Blood sample, which is then sent to central laboratory.
    - Antineoplastic therapy.
    - Assessment of concomitant medications.
    - Assessment of adverse events.
    - Tumor evaluation: CT, PET-CT and MRI of at least the chest and abdomen.
    - Survival.
    - Tumor re-biopsy will be considered (as recommendation only) for analysis of possible mechanisms of resistance and future translational research at the reference laboratory.

5.5 Discontinuation of patient, study or site participation

Treatment discontinuation: Patients have the right to withdraw from the study at any time and for any reason, without being required to state their reasons for doing so. The investigator has the right to discontinue a patient from study treatment or from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study, for reasons of non-compliance (e.g., missed doses, visits), if the patient becomes pregnant, or if the investigator determines it is in the best interest of the patient.

Patients should be withdrawn from the study treatment if they experience disease progression as defined by RECIST v1.1 criteria. An exception to this are patients who develop isolated brain progression as described in section 3.4, and who, in the investigator's judgment, will clinically benefit from the drug.

Further details regarding study discontinuation due to side effects are described in section 7.

Patients who withdraw from study treatment prematurely will be followed up in accordance with section 5.3 except for those patients who withdraw their consent and who do not wish to undergo a follow-up. The main reason for discontinuation should be recorded in the appropriate section of the case report form (CRF).

Study discontinuation: Section 3.7 defines EoS and study discontinuation.

Patients will be withdrawn from the study (e.g., from any subsequent study procedure) for any of the following reasons:

- Withdrawal of consent.
- Lost to follow up.

If patient is lost to follow-up, site personnel must do their utmost to re-establish contact with the patient and determine the reason for their withdrawal. All measures taken to undertake follow-up should be recorded.

When a patient withdraws before the end of the study, the reason for withdrawal should be recorded in the CRF and in the original document. Patients who withdraw from the study will not be replaced.

In addition, the sponsor reserves the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health risk to patients.
- Patient enrollment is unsatisfactory.
- Decision of the Scientific Committee once results of interim analysis are known.
- Data recording is inaccurate or incomplete.

6 INFORMATION ON STUDY DRUG

6.1 Study treatment

Once enrolled in the study, the patient will receive study treatment.

The treatment dose will be one tablet of osimertinib (AZD9291) 80 mg for daily oral administration.

Tablets will be packed in child-resistant high-density polyethylene (HDPE) bottles. The bottles dispensed to patients will be specially prepared for the study.

6.2 Drug supplies

The latest version of study document Summary of Product Characteristics for osimertinib (AZD9291) includes updated information on this drug.

The drug will be supplied by AstraZeneca to the sponsor, who will be responsible for its distribution to participating hospitals until the end of study, which will be after 78 weeks of follow-up of the last patient enrolled. From this point onwards, patients may continue to receive the commercial drug, if your doctor considers it appropriate.

The sponsor will supply sites with HDPE (high-density polyethylene) bottles containing osimertinib (AZD9291) 80 mg tablets for oral administration and HDPE (high-density polyethylene) bottles containing osimertinib (AZD9291) 40 mg tablets for oral administration. The smaller dose tablets can be taken in cases that call for a reduction of the dose of osimertinib (AZD9291) under circumstances described in Section 6.9.

6.3 Formulation and packaging

The sponsor will supply drug formulation for oral administration to sites in HDPE (high-density polyethylene) bottles containing 80 mg or 40 mg tablets. Tablets will be packed in bottles with child-resistant closures. The bottles will be dispensed to patients in packages specially prepared for use in this study.

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The label text will be translated into the local language. The label will include the name of the sponsor, study code, text stating that the drug is for clinical trial use only and/or any other market-specific requirements. All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the pack will specify the appropriate storage.

6.4 Dispensation

The unique patient number (UPN) will be recorded on the label affixed to the box in the areas set aside for this information when drug is assigned to the patient. Site personnel should ensure that the patients fully understand the instructions given to them regarding self-administration. Patients should be given an adequate supply of the drug that will last until the following study visit. Any unused and/or empty bottles should be returned to the site during the next study visit. Unused medication that has been returned SHOULD NOT be supplied to patient.

Two doses of osimertinib (AZD9291), 40 mg and 80 mg tablets for oral administration, will be supplied. At each visit, sufficient osimertinib (AZD9291) for the following programmed cycles (21 days per cycle) to last until the next visit, + 4 additional days per cycle (overage) will be distributed. Individual bottles will be dispensed in accordance with the medication identification numbers provided by the sponsor. Subjects should swallow one osimertinib (AZD9291) 80 mg tablet once daily, commencing on Day 1 of each cycle.

At each dispensing visit, the patient will only receive tablets of one strength or the other, not both. In the event a dose change is required, the patient will be asked to return all previously supplied medication and new tablets will be supplied to them.

6.5 Administration

Patients will be treated with osimertinib (AZD9291) administered orally, once a day. The initial dose of osimertinib (AZD9291) is of 80 mg per day. Treatment with osimertinib (AZD9291) is continuous. Each 21-day treatment period represents one cycle, and treatment will begin on day 1 of the first cycle. Routine pre-medication is not recommended for osimertinib (AZD9291). In the event of relevant toxicity, dose reduction is recommended to improve tolerance.

At each visit, sufficient osimertinib (AZD9291) for the following programmed cycles (21 days per

cycle) to last until the next visit, + 4 additional days per cycle (overage) will be distributed. Individual bottles will be dispensed in accordance with the medication identification numbers provided by the sponsor. Subjects should swallow one osimertinib (AZD9291) 80 mg tablet once daily, commencing on Cycle 1 Day 1.

Tablets will be taken once daily and may be taken with or without food. The tablet should be swallowed whole with water and should be crushed, split or chewed.

If the patient cannot swallow the tablet, it may be diluted in 50 mL of non-carbonated water and immediately swallowed. Subsequently, the patient should refill the glass with water and swallow it again in order to take the full dose. No other liquid may be added for this purpose.

In case of administration via nasogastric feeding tube, the same process described above should be carried out using volumes of 15 mL for the initial dilution and 15 mL to clean the potential medication waste. The remaining 30 mL should be administered via nasogastric feeding tube appropriately according to the manufacturer's instructions. This alternative administration should be carried out until a maximum of 30 minutes upon dilution.

The initial dose of 80 mg AZD9291 can be reduced to 40 mg AZD9291 once daily, under circumstances described in Section 6.9. Doses should be taken approximately 24 hours apart at the same time point each day. If a subject misses a scheduled dose, it is acceptable to take the dose within a window of 12 hours. If it is more than 12 hours after the dose time, the missed dose should not be taken, and subjects should be instructed to take the next dose at the next scheduled time. If a subject vomits after taking their osimertinib (AZD9291), they should not make up for this dose, but should take the next scheduled dose. Any change from dosing schedule, dose interruptions, and dose reductions should be recorded in the CRF.

Drug treatment is to begin within 2-4 weeks of reception of the tumor sample at the central reference laboratory. Patients will continue receiving the assigned therapy until objective disease progression, symptomatic deterioration, occurrence of an unacceptable side effect, death, withdrawal of consent or the end of the trial (78 weeks from the first dose of the last enrolled patient), whichever occurs first.

However, patients may continue to receive treatment with commercial osimertinib (TAGRISSO) according to the investigator's judgment. In this case, the investigator should follow-up on the patient in an appropriate manner, according to standard clinical practice.

6.6 Medication errors and overdose

Medication errors in this study may arise when the drug is administered at the wrong time or when the wrong dose strength is taken. Patient medication errors should be recorded in the relevant section in the CRF. In the event of an error in the administration of the medication, the sponsor should be informed immediately.

Medication errors must be reported irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational medicinal product;
- Any possible medication errors or use of the medication not defined in the protocol which implicate the participating patient or not.

Regardless of whether the medication error is accompanied by an AE or not, in the judgment of the investigator, the medication error should be recorded in the adverse event (AE) page.

6.7 Treatment compliance

At the beginning of each cycle, patients will be required to return all bottles of osimertinib (AZD9291) for drug count. The members of the study staff are responsible for counting osimertinib (AZD9291).

Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug for the next cycle. The number of remaining tablets will be documented and recorded.

To be considered compliant, each study patient must have received at least 80 % of the planned number of doses of primary treatment based on the number of days of actual dose administration. If a dose titration is required, see instructions provided in section 6.9.

6.8 Drug storage and accountability

Investigators and site personnel are reminded to continuously observe storage temperatures and to verify the correct operation of thermometers, as required for the correct storage of the investigational product. This includes thermometers for room temperature storage and thermometers for fridge storage.
At the end of the study, the sponsor will give instructions regarding the disposal of unused investigational products. If the sponsor authorizes the destruction of medication at the study site, the investigator should ensure that the materials are destroyed in accordance with the relevant environmental regulations, institutional policy and any special instructions given by the sponsor. The destruction of these materials will be recorded in an appropriate manner.

6.9 Dose change

Every effort should be made to administer study treatment based on the planned dose and regimen. Nevertheless, in the event of a significant treatment-related side effect, an adjustment can be made in the administration of the study drug as described in the following sections.

In case of toxicity, symptomatic treatment and dose changes should be made according to the following instructions. Repeated dose interruptions are allowed as required, for a maximum of 3 weeks each time (a delay of up to 3 weeks after the planned drug administration is allowed). As long as the study drug administration can be continued, the patient will remain on trial treatment. In case of doubt, please contact the medical monitor immediately.

6.9.1 Dose reduction

In the event of a significant treatment-related side effect, the osimertinib (AZD9291) dose can be interrupted, delayed and/or reduced, as described below. In the event of multiple side effects, dose change should be based on the worst toxicity observed. Patients are instructed to notify the investigator the moment he/she notices any adverse signs or symptoms.

After an interruption in administration or a delay in a cycle, a dose reduction may be necessary when treatment is to be resumed. No specific dose adjustments are recommended for Grade 1 or 2 treatment-related toxicity.

However, investigators should always use their judgment when treating patients, in accordance with the specific clinical circumstances. A reduction in osimertinib (AZD9291) dose by 1 dose level (Table 2) is permitted, based on the type and severity of the side effect. Patients requiring more than 1 dose reductions will be discontinued from the study and entered into the follow-up phase. All dose changes/adjustments should be clearly noted in the original patient record and in the CRF.

Table 2. Osimertinib (AZD9291) dose reduction

Dosing level	Osimertinib (AZD9291) for 3 weeks
Starting dose	80 mg/day
- 1	40 mg/day
	Discontinue study treatment

Table 3. Osimertinib (AZD9291) dose adjustment after adverse reactions

Organ involved	Adverse Reaction	**Dose change**
Lung	ILD/Pneumonia	Discontinue the treatment . permanently.
Heart	QTc interval >500 ms at least in 2 different ECGs.	Maintain of osimertinib (AZD9291) until the QTc interval <481 ms or go back to baseline results if they are ≤481 ms and then, restart at a reduced dose (40 mg).
	QTc interval prolongation with signs/symptoms of severe arrhythmia.	Discontinue osimertinib (AZD9291) permanently.
Other	Grade 3 or higher adverse reaction.	Discontinue osimertinib (AZD9291) up to 3 weeks.

	If the grade 3 adverse reaction improves to grade 2 or lower after osimertinib discontinuation up to 3 weeks	The administration of osimertinib (AZD9291) may start at a normal dose (80 mg) or at a reduced dose (40 mg).
	If the grade 3 adverse reaction improves to grade 2 or lower after osimertinib discontinuation up to 3 weeks.	Discontinue osimertinib (AZD9291) permanently.

6.9.2 Interruption of administration

The dose may be interrupted, when necessary, until the resolution of toxicity. Depending on when the adverse event is resolved, an interruption in therapy may cause the patient to miss subsequent doses that have been scheduled for that cycle and even delay the start of the next cycle.

Administration of osimertinib (AZD9291) should be permanently discontinued under the following circumstances:

- Interstitial pneumonitis.
- Hepatic insufficiency.
- Gastrointestinal perforation.
- Corrected QT interval prolongation with signs/symptoms of severe arrhythmia.
- Suspension of treatment lasting more than 3 weeks.

If the adverse event that gave rise to the interruption of treatment is resolved within that same cycle, the treatment can be resumed in that cycle. Doses not administered due to toxicity will not be replaced in that same cycle. The need for a dose reduction when treatment is to be resumed should be assessed in keeping with the criteria defined above, unless otherwise agreed upon by the investigator and sponsor. If a dose reduction is made within the cycle, the patient should come to the site to receive a new supply of the drug. If the treatment is interrupted for reasons other than treatment-related toxicity (e.g., surgery not related to cancer) for a period >2 weeks, treatment can only be resumed after consultation with the sponsor.

The appropriate follow-up assessments should be performed until adequate resolution has been reached, in the judgment of the investigator. If these parameters are not met within 3 weeks after the dose interruption (including the scheduled treatment week during which the patient did not receive treatment), then the treatment should be considered permanently discontinued. Treatment can be resumed in cases where patients have recovered from a treatment-related side effect after a period in which treatment has been discontinued for more than 3 weeks or after the cycle has been delayed, but only if treatment offers a clinical benefit to the patient in the judgment of the investigator. In these cases, it is left to the discretion of the investigator after consultation with the sponsor.

If a new cycle is delayed owing to a treatment-related side effect, all procedures other than tumor assessments that are outlined in the protocol and required on Day 1 of the cycle will be performed when treatment with osimertinib (AZD9291) is resumed. Note that the protocol schedule must be followed for tumor assessments. The procedures performed on Day 1 of a new cycle (i.e. physical examination, ECOG performance status, ECG, blood chemistry,

blood count) that were performed before awareness of the need to delay the start of the cycle do not need to be repeated (1) if the study staff does not need to determine whether study drug can be resumed and (2) if they were performed within 7 days prior to resuming the study drug.

6.10 Possible drug interactions

In vitro data indicate that osimertinib (AZD9291) is mainly metabolized via CYP3A4. Patients should avoid using drugs that are strong inhibitors or inducers of cytochrome p450 (CYP)3A4 during the study active phase. Patients should also avoid grapefruit juice and herbal remedies, including St John's Wort. If their use is essential, patients who are taking them should be monitored closely.

Drugs listed in Appendix 3: Pharmacological interactions with osimertinib (AZD9291) are not permitted due to their drug interaction with the study drug.

Patients who use drugs that are known to prolong the QT interval should be closely monitored using serial electrocardiograms.

7 STATISTICAL CONSIDERATIONS AND STATISTICAL ANALYSIS PLAN

7.1 Sample Size

In the Phase I/II AURA clinical trial, where osimertinib (AZD9291) was administered to patients with advanced EGFR-mutant NSCLC after progression to EGFR TKIs, among the 127 patients with centrally confirmed EGFR T790M mutation, the response rate was 61%. In contrast, amongst 61 patients without centrally confirmed EGFR T790M, the response rate was 21% (15). In the West Japan Thoracic Oncology Group 3405 (WJTOG3405) study, comparing gefitinib with first-line chemotherapy in patients with advanced NSCLC with activating mutations in EGFR, the ORR in the overall population with measurable disease was 62.1% in the gefitinib group and 32.2% in the chemotherapy group. In the North East Japan 002 (NEJ002) study, comparing gefitinib with first-line chemotherapy in patients with advanced NSCLC with EGFR mutations, the gefitinib group had a significantly higher ORR (73.7% vs. 30.7%). In the OPTIMAL study, comparing erlotinib with chemotherapy in patients with advanced NSCLC with EGFR mutations, ORR was 83% for erlotinib and 36% for patients receiving chemotherapy (37). In the LUX-Lung 3 study, comparing afatinib with first-line chemotherapy in patients with advanced NSCLC with EGFR mutations, ORR was significantly higher for patients treated with afatinib compared to chemotherapy according to both the independent evaluation committee (56% and 23%, respectively) and the investigator (69% and 44%, respectively) assessments. In the EURTAC study, comparing erlotinib with first-line chemotherapy in patients with advanced NSCLC with EGFR mutations, ORR was 65.1% in the erlotinib group and 16.1% in the chemotherapy group. A subsequent study assessed the impact of pre-treatment presence of the concomitant EGFR T790M mutation. Among patients treated with erlotinib, the presence of this concomitant mutation was evaluated in 95 patients. ORR was found to be 75% in patients without pre-treatment T790M, compared to 47% in patients with pre-treatment T790M.
This data suggests that excluding an ORR ≤50% while targeting the improvement of the ORR to ≥70% would be a conservative approach to assess the osimertinib (AZD9291) treatment effect in this patient population. Accordingly, this study will test the null hypothesis that the ORR is ≤50% against the alternative hypothesis that it is ≥70%. Applying Simon's optimum 2-stage

design [Simon 198940], a sample size of 73 patients has power >0.90 to achieve a 1-sided significance level of 0.025. A total of 21 patients will be recruited in the first stage. If there are 11 or fewer responses in these 21 patients, the study will be stopped. Otherwise, 52 additional patients will be accrued for a total of 73 patients. The null hypothesis will be rejected if 45 or more responses are observed in 73 patients. This design yields a type I error rate of 0.025 and a power of 90% when the ORR is 70%.

8.2 Efficacy results

Primary Endpoint

We will describe number and proportion of patients with OR (Objective Response) in the first and second stages. We will estimate the proportion of responders with Clopper-Pearson 95% confidence intervals. We will estimate the uniformly minimum variance unbiased estimator (UMVUE), p-value and 95% confidence interval.

Secondary endpoints:

Number and percentage of patients who obtain Complete Response, Partial Response, Stable Disease and Disease Progression will be provided. The Objective Response Rate (ORR) and its 95% confidence interval (CI) will be calculated. The Disease Control Rate (DCR) and its 95% CI will be calculated. Progression-free Survival (PFS), Overall Survival (OS), Time to Treatment Failure (TTF) and Duration of Response (DOR) will be considered secondary objectives, and as they are time objectives, they will be analyzed using the Kaplan-Meier method. The number and proportion of events and median survival time with their corresponding 95% CIs will be calculated. The analyses will be supported by graphical presentations such as survival plots.

Difference between baseline tumor measurements and those observed throughout the study will be analyzed using the Wilcoxon test. The average percentage of Tumor Shrinkage (TS) observed from baseline to study visits, with their corresponding 95% CIs, will be calculated. Patients with and without different types of EGFR mutation will be compared. For binary outcomes (ORR and DCR), the chi-square or Fisher's exact test will be used. For time objectives (PFS, OS, TTF and DOR), the Kaplan-Meier method and log-rank test will be used. For continuous objectives (percentage of Tumor Shrinkage, TS), the Mann-Whitney U test will be used.

Baseline biomarker levels will be correlated with the clinical response. For binary and continuous results, the Spearman correlation will be used. For time objectives (PFS), the Kaplan-Meier method and log-rank test will be used. The categorization or log-transformation of biomarker levels will be considered.

The feasibility of re-biopsies at the time of progression will be estimated with the number and percentage of patients with rebiopsy and 95% confidence interval.

The presence of mutations and biomarker levels (tissue or blood) will be compared from baseline to time of progression with the Mc Nemar and Wilcoxon tests, respectively.

All efficacy analyses will be exploratory. Positive results in this trial will not confirm treatment efficacy, however, they will indicate that osimertinib (AZD9291) might be considered in the supportive tests.

8.3 Safety results

Analysis of safety-related data will be considered at three levels:

- First, the degree of exposure (dose, duration, number of patients) will be assessed to determine the degree to which study safety can be assessed.
- Second, clinically relevant tests, concomitant medications and reported adverse events for each study group will be described and compared. For adverse events, severity, expectedness, causality, relationship, body system, action taken, and outcome will be reported.
- Third, serious adverse events, deaths and study discontinuations for each study group will be described and assessed.

8.4 Populations for analysis

Full population for efficacy and safety analysis

It includes all patients who have received the investigational treatment, regardless of the degree of compliance with the protocol.

Per-protocol population (PP):

Per-protocol population includes all patients of the full population for analysis that have not presented any protocol violations that may affect the assessment of the primary endpoint of the study (major protocol violations).

Population for biomarker analysis

All patients included in the full population for analysis whose biomarkers have been assessed.

Efficacy analyses are performed on the full population for analysis and the per-protocol population. The full analysis set population will be the primary population for the efficacy analyses.

The biomarker analysis will be performed on the population for biomarkers. The

safety analysis will be performed for the full analysis population.

8.5 Missing data management

We will report the number of missing values for each endpoint. Patients with missing values in the primary analysis and clinical response outcomes (ORR and DCR) will be considered non-responders. The analysis of time-dependent secondary endpoints (progressions, treatment failures and deaths) will be based on a log-rank test or on Cox regression tests and therefore, will not be affected by the withdrawal of patients (as they would be censored), provided that withdrawals are not related to the prognosis. Patients with missing data regarding endpoints, such as objective response, will be considered patients with no response to treatment. In addition, we will report the reasons for withdrawal of each patient assigned to the treatment.

8.6 Interim analysis

An interim analysis will be performed when 21 patients have been assessed up to 42 weeks or have withdrawn from the study. The interim analysis will assess the primary endpoint and all the secondary safety and efficacy objectives limited to a window of up to 42 weeks. However, after the database lock at 42 weeks, these patients will continue to be treated and followed up in the study until the patient progresses, dies, discontinues the treatment or completes the study, whichever occurs first.

The efficacy and safety results of the interim analysis will be evaluated by a Scientific Committee that will decide on the suitability of continuing with the study. The study will only be interrupted in case of futility or for safety reasons. For this test, significance levels with p-values with alpha error ≤0.025 will be used.

8.7 Scientific Committee Review

A Scientific Committee (SC) has been appointed for this study. Initially, the committee consists of the investigators, the study Medical Monitor and two physicians specialized in osimertinib (AZD9291) therapy.

The SC will meet on demand to review, discuss and evaluate all of the collected safety data. In the event of a safety issue, a meeting can also be called at any time at the request of an investigator participating in the study. At these meetings, MedSIR and the participating investigators must reach a consensus on safety data. MedSIR will prepare minutes for these meetings and submit them to each investigator for comment prior to finalization.

The study site Investigators and MedSIR will review patient data at least every four months. Each study site investigator will regularly review patient data to detect serious side effects.

8 ETHICAL CONSIDERATIONS

9.1 Regulatory and ethical compliance

The study will be conducted and reported in accordance with the protocol, the International Conference on Harmonization (ICH) Guidelines, and the ethical principles laid down in the Declaration of Helsinki. The study will also comply with European Regulation No. 536/2014 and any applicable local regulations.

9.2 Ethics Committee:

The conduct of the study must be authorized by a duly constituted EC. Authorization is required for study protocol, protocol amendments, informed consent forms, patient information sheets and promotional materials.

Wherever necessary, the investigator and/or sponsor should contact the EC to ensure that accurate and timely information is being provided at every phase of the study.

The principal investigator and/or sponsor are responsible for providing, when required, written summaries of the study status to the EC annually or more frequently, in accordance with the requirements, policies and procedures set out by the EC.