Statistical Analysis Plan

1. TITLE PAGE

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

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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

95%CI	95% confidence interval
AE	Adverse Event
ALT	Alanine transferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BOR	Best overall response
cORR	Confirmed overall response rate
CNS	Central nervous system
CR	Complete response
CRF	Case Report Form
CTCAE	Common terminology criteria for adverse events
DCR	Disease control rate
DoR	Duration of response
ICH	International conference of harmonisation
ECG	Electrocardiography
ECOG	Eastern cooperative oncology group
EGFR	Epidermal growth factor receptor
EORTC	European organisation for research and treatment of cancer
HIV	Human immunodeficiency virus
IC	Informed consent
IMP	Investigational Medical Product
ILD	Interstitial Lung Disease
LNL	Lower normal limit
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
N	Number of patients
NA	Not applicable
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
OR	Overall response
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PET-CT	Positron emission tomography/computed tomography
PMF	Probability of mass function
PR	Partial response
RECIST	Response evaluation criteria in solid tumours
SAP	Statistical Analysis Plan
SC	Steering committee
SD	Stable disease
TTF	Time to failure
TS	Tumor Shrinkage
UMVUE	Uniformly minimum variance unbiased estimator
UNL	Upper normal limit
US	United states

3. VERSION HISTORY

(Versions before data base lock)

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APPROVAL

The signing parts declare to have seen and revised this document and approve its content. *(Draft versions do not require signed approval).*

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4. INTRODUCTION

4.1 Preface

We can state that in EGFR-mutation-positive NSCLC, in addition to the molecular diagnosis, it is necessary to quickly validate and implement a kit as part of clinical practice for the detection of a predictive biomarker panel that will allow for adequately personalized treatments using EGFR TKIs in monotherapy. To this end, we propose to begin a phase IIa clinical trial of osimertinib (AZD9291) in patients with a recent diagnosis of NSCLC with EGFR mutations and with the concomitant pre-treatment T790M mutation. The mutation will be detected in tumor tissue using a highly sensitive assay for T790M, based on laser microdissection and a peptide-nucleic acid clamping PCR.

4.2 Purpose of the analyses

These analyses will assess the efficacy and safety of osimertinib (AZD9291) in patients with advanced non-squamous NSCLC with EGFR mutations and the EGFR T790M mutation at diagnosis.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1 Study objectives

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, as defined by RECIST 1.1 criteria.

5.2 Endpoints

(ICH E9; 2.2.2)

The efficacy study endpoints will be deribed in accordance with Per Response Evaluation Criteria in Solid Tumours (RECIST v1.1) assessed by magnetic resonance imaging (MRI) or computed tomography scan (CT). The next endpoints has been defined:

Complete Response (CR): Disappearance of all target and non-target lesions and no new lesions.
Partial Response (PR): >= 30% decrease in the sum of diameters of Target Lesions (TL) (compared to baseline) and no new lesions.

Stable disease (SD): Neither sufficient shrinkage to qualify as a response nor sufficient growth to qualify as progression.

Progressive Disease (PD): >= 20% increase in the sum of diameters of TLs and an absolute increase in sum of diameters of >=5mm (compared to the previous minimum sum) or progression of NTLs or a new lesion.

Not evaluable (NE): TL response is missing and there is no evidence of progression of NTLs and no new lesions.

BOR is the best response (by investigator assessment) a patient has achieved where the order of best to worst is CR, PR, SD, PD, NE prior to or at progression and prior to further anti-cancer therapy.

Additionally censoring strategies in time to event outcomes will be defined in accordance with Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics from dood and drug administration.

5.2.1 Primary endpoint

Confirmed objective response rate (cORR) is defined as the number of patients with complete response (CR) and partial response (PR), confirmed at least 4-6 weeks after the initial response, divided by the number of patients in the analysis set. Tumor response will be defined as best response, based on local investigator's assessment according to RECIST criteria guidelines (version 1.1).

5.2.2 Secondary endpoints

The following exploratory endpoints will be analysed:

- Objective response rate (ORR) is defined as the number of patients with complete response (CR) and partial response (PR) divided by the number of patients in the analysis set. Tumor response will be defined as best response, based on local investigator's assessment according to RECIST criteria guidelines (version 1.1).
- Disease control rate (DCR) is defined as the patients with CR, PR, or SD relative to all participants in analysis set. Participants who do not have on-study radiographic tumor reevaluation, who received anti-tumor treatment, who died, progressed, or dropped out for any reason prior to achieving reaching a CR or PR and a best response of SD was counted as non-responders in DCR.
- The progression-free survival (PFS) as assessed by investigator is defined as the time from the date of randomization to the date of the first documentation of objective tumor progression as per RECIST v1.1 or death due to any cause in the absence of documented PD, whichever occurs first. If tumor progression data include more than 1 date, the first date will be used. PFS (in months) will be calculated as (first event date − randomization date +1)/30.4. Progression is defined using RECIST v1.1, as a 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm, or unequivocal progression of pre-existing non-target lesions, or the appearance of new lesions.
- Overall survival (OS) is defined as the time from treatment start to the time of death due to any cause.
- Time to treatment failure (TTF) is defined as the time from treatment start to the time at which the patient discontinues treatment due to any cause, including disease progression assessed by the investigator as per RECIST v1.1, toxicity, death or at the patient's request.
- Duration of response (DOR): is defined as the time from the date of first documented response (CR or PR that was subsequently confirmed) until the date of documented progression (PD) or death in the absence of disease progression (by investigator assessment).
- 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) per RECIST v1.1 criteria.

5.2.3 Exploratory endpoints

The following exploratory endpoints will be analyzed:

- 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.

5.2.4 Safety endpoints

The following safety endpoints will be analyzed:

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.

6. STUDY DESIGN

6.1 General study design and plan

(ICH E3;9.)

Identify the study design, including the following:

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

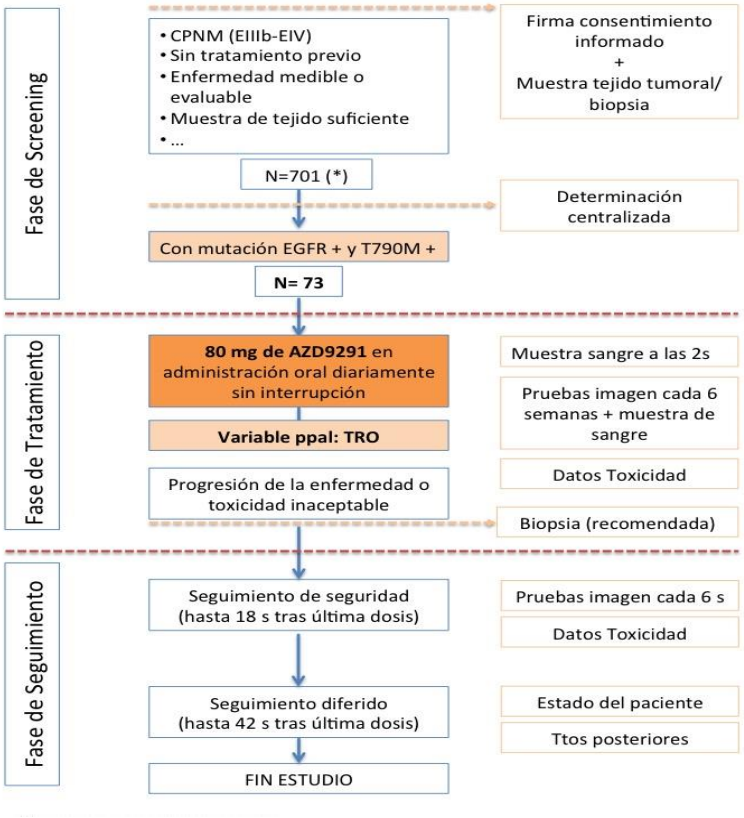
- **Treatment phase:**

When a patient carrying 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.
- 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 study protocol non-compliance.
- Patient's withdrawal from the study.
- Dead.
- After a maximum of 78 weeks from the patient first study treatment dose intake.
- Study is canceled by the Sponsor.

- **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.



6.2 Visits schedule

(ICH E3; 9.5.1. ICH E9; 2.2.2)

The following table presents the relation between visits and medical assessments planned for this study:

SAP Table. 1 Visits schedule

Assessment	Screening	Baseline	Treatment period: 2 -weeks post-baseline evaluation	Treatment period: Complete evaluations	Treatment period: Routine evaluations	End of treatment visit: After progression or at the end of treatment for any other reason	Follow-up
	(2-4 weeks as maximum before baseline)	Day 0 (pre-treatment)	After 2 weeks	After 12, 24, 36, 48, 60, 72 weeks from first dose	After 6, 18, 30, 42, 54, 66, 78 weeks from first dose	Within 4 weeks after end of treatment (only if end of treatment is not confirmed in some of the scheduled full visits)	After progression or end of treatment for any other reason, after 12,24,36,48, 60, 72, 78 weeks after first dose
Written Informed Consent	**X**						
Sample (tissue) to the central lab	**X** [1]					**X (if available)**	
Medical History		**X**		**X**			
Physical examination, ECOG Performance Status, Vital Signs, body weight		**X** [2]		**X** [2]	**X** [2]	**X** [2]	
Recording of symptoms		**X**		**X**	**X**	**X**	
Pregnancy Test		**X** [3]					
Hematology		**X** [4]		**X** [4]	**X** [4]	**X** [4]	
Renal function		**X** [4]		**X** [4]	**X** [4]	**X** [4]	
Blood Chemistry		**X** [4]		**X** [4]	**X** [4]	**X** [4]	
Coagulation		**X** [4]		**X** [4]	**X** [4]	**X** [4]	
Urine dipstick test for analysis of proteinuria		**X** [4]		**X** [4]	**X** [4]	**X** [4]	
ECG		**X** [5]		**X**	**X (only if clinically required)**	**X**	
Tumor Assessment		**X** [6]		**X** [6]		**X** [6]	

Serum/plasma sample for translational research		**X**	**X**	**X**		**X**	
Antineoplasic therapy		**X**	**X**	**X**	**X**	**X**	**X**
Concomitant Medication	X		**X** [7]	**X** [7]	**X** [7]	**X** [7]	
Adverse Events			**X**	**X**	**X**	**X**	**X** [8]
Survival			**X**	**X**	**X**	**X**	**X**

1. EGFR results from test performed locally in the same laboratory than the central one up to 28 days before inclusion will be accepted.
2. Vital signs include pulse and temperature.
3. A negative serum or urine pregnancy test up to 7 days before inclusion will be accepted.
4. Hematology, renal function, blood chemistry and coagulation tests performed up to 72 hours before inclusion and before the corresponding date of each visit will be accepted.
5. ECG performed up to 14 days before inclusion and before the corresponding date of each visit will be accepted.
6. Assessment procedures should be the same at every visit. Baseline tumor assessments should include, at least, chest and abdominal CT. If, in the opinion of the investigator it is clinically indicated, other radiological evaluations may be performed (PET-CT, MRI). PET-CT, MRI performed up to 28 days before inclusion and up to 14 days before every visit during treatment period including end of treatment visit will be accepted
7. Every concomitant medication will be recorded, including analgesics.
8. Every new AE identified up to 28 days after administration of last dose of study treatment or until a maximum of 78 weeks after first dose should be recorded on the corresponding CRF page (AE).

6.3 Study population

(ICH E3;9.3. ICH E9;2.2.1)

Patients diagnosed with stage IIIB or IV non-small cell lung cancer carrying the EGFR activating mutation and confirming concomitant T790M mutation during screening 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.

6.3.1 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 locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC) with an activating EGFR mutation and concomitant T790M mutation who are not candidates for local curative treatment.
3. Patients with a 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 a 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 (as per 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, within the 60 days prior to study entry.
8. Life expectancy ≥12 weeks.
9. Adequate hematologic function: Absolute neutrophil count (ANC) > 1.5 x 10^9/L, platelet count > 100.0 x10^9/L and hemoglobin > 9.0 g/dL (> 6.2 mmol/L).
10. Adequate 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 (Cockroft-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.

6.3.2 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 a EGFR deletion or mutation in exon 19, exon 21 (L858R, L861Q) or exon 18 (G719X) and concomitant 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 msec, obtained from 3 ECGs 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 HIV or heart disease) that is incompatible with the study (in the opinion of the investigator), history of bleeding diathesis or anticoagulant therapy (the use of low molecular weight heparin is permitted provided that it is used for prophylaxis).
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 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 chemotherapy for advanced NSCLC; neoadjuvant/adjuvant chemotherapy is permitted if at least 6 months have elapsed between the end of 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 the first day of study treatment.
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.

6.4 Sample size

(ICH E3; 9.7.2. ICH E9; 3.5)

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 (C. Zhou et al. 2011). 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, R 1989), a sample size of 73 patients has power > 0.90 to achieve a 1-sided significance level of 0.025. In the first stage, 21 patients will be accrued. 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%. The recruitment will be competitive between sites.

6.5 Randomization and blinding

(ICH E3; 9.4.3, 9.4.6. ICH E9; 2.3.1, 2.3.2)

No applicable.

6.6 Interim analysis

An interim analysis will be performed when 21 patients have been assessed up to 42 weeks or 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. The first interim report will only include the summary of study accrual, the clinical and demographic summary, the primary efficacy analysis and the report of toxicity. This first report has developed to not delaying the go/not go decision in the first stage. The other results will be presented later. After the database

lock at 42 weeks, these patients will continue to be treated and monitored until progression, death or treatment discontinuation. The decision to stop and continue the trial should be agreed by the steering committe after reviewing the interim safety and efficacy data.

6.1 Final analysis

Upon completion of the interim analysis, and according to the evaluation of the results obtained during the interim analysis, recruitment of patients will resume until a total of 73 patients have been recruited during a 24-month recruitment period. A follow-up lasting up to 78 weeks will begin upon the first dose had been administered to each patient. The study will end, at latest, 78 weeks after last patient has started the treatment.

7. STATISTICAL METHODS

7.1 Primary analysis

We will describe number and proportion of patients with cOR (confirmed 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.

Point estimation according UMVUE:

$$\bar{p}=\begin{cases} s/n_1 & \text{if } m=1 \\ \dfrac{\sum_{x1=(a1+1)\vee(s-n2)}^{s\wedge(b1-1)}\binom{n1-1}{x1-1}\binom{n2}{s-x1}}{\sum_{x1=(a1+1)\vee(s-n2)}^{s\wedge(b1-1}\binom{n1}{x1}\binom{n2}{s-x1}} & \text{if } m=2 \end{cases} \qquad \textbf{(Equation 1)}$$

Probability of mass function (PMF) according UMVUE:

$$f(m,s|p)=\begin{cases} p^s(1-p)^{n1-s}\binom{n1}{s} & \text{if } m=1,\ 0 \leqslant s \leqslant a_1 \text{ or } b_1 \text{ or } b=1 \\ p^s(1-p)^{n1+n2-s}\sum_{x1=(a1+1)}^{s\wedge(b1-1}\binom{n1}{x1}\binom{n2}{s-x1} & \text{if } m=2,\ a_1+1 \ \ s \leqslant b_1 - 1 + n_2 \end{cases} \qquad \textbf{(Equation 2)}$$

P-value according UMVUE:

$$\text{p-value}= \begin{cases} \sum_{j=s}^{n1} f(1,j|p0) & \text{if m = 1, s} \geq 1 \\ 1- \sum_{j=0}^{s-1} f(1,j|p0) & \text{if m = 1, s} \geq 1 \\ \sum_{j=b1}^{n1} f(1,j|p0) + \sum_{j=s}^{b1-1+n2} f(2,j|p0) & \text{if m = 2} \end{cases} \quad \textbf{(Equation 3)}$$

Where:

M = study stage (1 or 2); p = effect of treatment as rate; p0 = expected effect of treatment considered as futility; a = maximum number of responders to accept null hypothesis at final analysis; a1 = maximum number of responders to accept null hypothesis at interim analysis; $b_1 = n_1+1$ for Simon's two-stage designs; s = the observed number of responding patients; n = expected number of patients included in the study; n1 = patients included in stage 1; n2 = patients included in stage 2; $a \wedge b = \min(a, b)$; $a \vee b = \max(a, b)$; $x! = x \times (x - 1) \times \ldots \times 2 \times 1$.

7.2 Secondary analysis:

Number and percentage of patients who obtain Complete Response, Partial Response, Stable Disease and Disease Progression will be provided. The Objective Response Rate (ORR), unconfirmed and confirmed 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. The average percentage of Tumor Shrinkage (TS) observed from baseline to study visits, with their corresponding 95% CIs, will be calculated.

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.

7.3 Safety analysis:

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.

7.4 Analysis populations

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 5.2)

Full Analysis and Safety analysis set (FAS)

Includes all included subjects who have received any study drug, independently of the degree of adherence to the protocol.

Per Protocol Set (PP)

The Per Protocol set includes all patients included in the FAS who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug on the primary endpoint, i.e., without a major protocol violation.

Major and minor protocol violations will be identified by clinically trained personnel before the database lock. The definition of the major protocol violations is described in **Appendix 2**.

Biomarker analysis set

All patients included in FAS who has been evaluable for biomarker status.

Sensitivity analysis

Primary efficacy analysis will be performed on the full analysis (FAS) and PP sets. Secondary efficacy analysis will be performed on FAS. FAS will be considered the primary population for the efficacy analysis.

Biomarker analysis will be performed on biomarker analysis set.

Safety analysis will be performed on the full analysis set.

7.5 Covariates and subgroups

(ICH E3; 9.7.1, 11.4.2.1. ICH E9; 5.7. CPMP 2002; 4.CPMP 2003.)

Difference between baseline tumor measurements and those observed throughout the study will be analyzed using the Wilcoxon test. Patients with and without different types of EGFR mutation will be compared. For binary outcomes (cORR, 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.

7.6 Missing data

(ICH E3; 9.7.1, 11.4.2.2. ICH E9;5.3. EMA Guideline on Missing Data in Confirmatory Clinical Trials)

We will report the number of missing values for each endpoint. Patients with missing values in the primary analysis and clinical response outcomes (cORR, 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 also report the reasons for withdrawal for each allocated patient.

7.7 Multi-centre studies

(ICH E3;9.7.1, 11.4.2.4. ICH E9; 3.2)

Individual centre results will be analysed combined in a single cohort. In accordance with previous experiences we assume that the center will not have relevant effect on safety or the activity of the study treatment.

7.8 Multiple testing

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 2.2.5)

All efficacy analyses will be exploratory. Positive results in this trial has not a confirmatory meaning, however, they will indicate that osimertinib (AZD9291) might be considered in the supportive tests. However the statistical design was based on a superiority binomial test of ORR. The statistical test has 90% power to detect a 20% increase over 50% ORR observed with other strategies in previous studies. The total type I error was adjusted in accordance with the stopping boundaries constraints in a Simon Two-stage design. The design yields a type I error rate of 0.025.

All secondary efficacy analysis has been considered supportive of primary endpoint and we have not planned a formal correction of the alpha error due to multiple testing.

Subgroup analysis has been considered exploratory, too. However, multiplicity issues derived from analysing multiple hypothesis will be adjusted by the Q-value index at 10% nominal level, based on (Storey JD, Bass AJ, Dabney A and Robinson D (2018). qvalue: Q-value estimation for false discovery rate control. R package version 2.14.0, http://github.com/jdstorey/qvalue).

7.9 Interim analyses and data monitoring

(ICH E3; 9.7.1, 11.4.2.3. ICH E9; 4.1, FDA Feb 2010 "Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics")

7.9.1 Purpose of interim analyses

We have planned an interim analysis to reduce the number of patients exposed if the therapeutic regimen investigated was inefficient or unsafe. We propose an interim analysis with a futility boundary, but not with efficacy boundary. The study will be only finished for primary outcome if the results are not promising. We do not want to stop the trial early for efficacy because we will recruit only a few patients at interim (21). The early discontinuation of the trial will impact negatively in the power of primary and secondary analysis if the combination is promising. However, the decision to stop and continue the trial should be agreed by the steering committee after reviewing the interim safety and efficacy data.

7.9.1 Stopping rules

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 (if there are 11 or fewer responses in these 21 patients) or safety (in case of any arising safety concern after steering committee review).

7.10 Decision rules and adjustment of alpha for primary endpoint at final analysis

The study will be declared positive if the following outcome are achieved:

1. Final analysis: The p-value estimated according stochastic ordering of uniformly minimum variance unbiased estimator (UMVUE) is <0.025. According with these criteria, if 73 patients are included in the analysis we will achieve a positive finding with 45 or more responders.

7.11 Steering 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 ARO and the participating investigators must reach a consensus on safety data. MedSIR ARO will prepare minutes for these meetings and submit them to each investigator for comment prior to finalization.

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

7.11.1 Adjustment of confidence intervals and p-values

The total type I error was adjusted in accordance with the stopping boundaries constraints in a Simon Two-stage design. The design yields a type I error rate of 0.025.

We account for the sequential nature of the design calculating the responder rate, confidence interval and p-values of primary endpoint in accordance with UMVUE method. The equation has been described in primary endpoint section.

7.11.2 Practical measures to minimize bias

This is an open label study with a descriptive purpose. All efficacy analyses will be exploratory. Positive results in this trial has not a confirmatory meaning. In accordance, the interim and final analysis will not be developed by different teams of statisticians. The decisions at interim analysis will be made by the steering committee and they will decide the information that will be publically available following the interim analysis.

7.11.3 Documentation of interim analyses

Snapshots of the data available at each interim analysis should be preserved, as should all documentation of analysis plans, programming code and reporting provided at each interim. It should be possible to recreate the decision process from the trial archive. Record what documents will be created and stored thus.

7.12 Reporting conventions

7.12.1 General reporting conventions

All tables, figures and data listings will be presented in portrait orientation, unless landscape orientation suggests that the information is easier to view. Legends will be used for all figures with more than one variable or item displayed. Figure lines should be wide enough to see the line after being copied.

Titles of all tables, listings and figures should contain the following information:

- Output number.
- Description of the data that is being summarized.
- Type of analysis performed, covariates used (if applicable).
- Analysis population.

7.12.2 Statistical summary conventions

For tables, sample sizes for each treatment group will be presented as totals in the column header (N=xxx), where appropriate. Sample sizes shown with summary statistics are the number (n) of patients with non-missing values.

Summaries for categorical variables will include only categories that patients had a response in. Percentages corresponding to null categories (cells) will be suppressed. All summaries for continuous variables will include: N, mean, and SD. Other summaries (e.g. median, quartiles, 5%, 95% intervals, range or interquartile range) will be used as appropriate. All percentages should be rounded and reported to a single decimal place (xx.x%). If percentages are reported as integers, percentages greater than 0% but <1% will be reported as <1%, whereas percentages greater than 99% but <100% will be reported as >99%. A percentage of 100% will be reported as 100%. No value of 0% should be reported. Any computation of percent that results in 0% is to be reported as a blank. P-values will be reported with three decimal places with a leading zero (0.001). P-values <0.001 will be reported as <0.001.

8. TECHNICAL DETAILS

Include a brief statement of: study-specific documents used, including version numbers; which software package or packages used; and the directory/file paths used to store data, code and output documents.

Describe what quality assurance measures are in place to monitor the quality of any coding. Document who will review which pieces of code, and to what level of detail. For example:

A second review statistician will independently reproduce the primary analyses. The reviewing statistician will have an overview of the entire.

9. SUMMARY OF CHANGES TO THE PROTOCOL

On December 17, 2018, the AZENT data monitoring committee, on review of the interim analysis, determined that there was evidence to support continued accrual, however the trial was closed to further accrual due to a funder's decision.

10. REFERENCES

Provide references for any citations in the main body of the SAP.

APPENDICES

Appendix 1. Handling of missing date and time fields

All dates and times used in the analysis are supposed to be complete. Nevertheless, in certain situations it will be difficult or impossible to have a complete date or time, e.g., lost to follow-up patients. SAP Table 3 contains a list of dates/times that will be completed in case of missing information.

General rules for completion of dates are the following:

1. Dates are split in 3 parts: year, month and day. Year is the top level, month is medium level and day is low level. If a part expected to contain a number is numeric but the value is outside a valid range, the complete date is handled as missing. For example, if date = 32-NOV-2012 the whole date is considered to be missing.

2. If a part expected to contain a number is not numeric, i.e., contains values such as, for example, ND, NA, 2? it is considered as missing.

3. If a part is missing, all other parts of a lower level are considered to be missing, e.g., '21-ND-2012' is considered as 'NK-NK-2012'.

4. Missing parts are changed into acceptable non-missing values depending on the type of date to be replaced.

In the following table, 'lower limit' and 'upper limit' refer to the minimum or maximum, respectively, of a possible date. For example, if the day is missing, the lowest limit is the first day of the given month and the upper limit is the last day of the given month. If the day and month are missing, the lower limit refers to the first day of the given year and the upper limit to the last day of the given year. The earliest and the latest of different dates refer to the first or last date, respectively, when ordered in sequence.

SAP Table. 2 Handling of missing data and time fields

Type of Date / Time	***Date /Time is incomplete***	***Date / Time is missing***
Date of birth	Day missing: 15th of the month Day and month missing: 30th of June	No replacement
AE resolution date	The upper limit	No approximation, the AE is considered as ongoing in the analysis.
AE onset date	If the end date of the AE is not before the start of study drug, and if the study drug start falls in the range of possible dates, it is the study drug start date. In all the other cases, it is the lower limit.	Earliest date between the AE end date and the start of study drug.
Hospitalization discharge date	The upper limit	No approximation, the hospitalization is considered as ongoing in the analysis.
Hospitalization admission date	If the onset date of the AE leading to hospitalization falls in the range of possible dates, it is the onset date of the AE. In all the other cases, it is the lower limit.	The onset date of the AE leading to hospitalization

Previous/ concomitant medication start date	Lower limit except when: Not tagged as ongoing at baseline AND Medication stop date not collected or with the upper limit after the study drug start AND the treatment start day falls in the range of possible dates. In which case it is the study drug start day	No replacement, the medication is considered to have started before the study
Previous/ concomitant medication end date	Upper limit except when: Medication start is before study drug start or missing AND Upper limit is after the study drug start AND Not tagged as concomitant at baseline. In which case it is 1 day before study drug start	No replacement (considered ongoing)
End of treatment	Use the earliest date between the: • upper limit • last contact date • date of death (if applicable)	Use the earliest date between the: • last contact date • date of death (if applicable)
Death date	Use the lower limit	No replacement

Appendix 2 List of protocol deviations

Description	**Category**	**Deviation excludes from analysis set?**		
		Full Analysis / safety set	**Per protocol set**	**Biomarker analysis set**
Informed consent form not signed	Inclusion/Exclusion criteria	Yes	Yes	Yes
Outdated versions of informed consent signed	Inclusion/Exclusion criteria	Case by case	Case by case	Case by case
IMP no administered	Treatment	Yes	Yes	Yes
Without histological confirmation of locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC).	Inclusion/Exclusion criteria	No	Yes	No
Without an activating EGFR mutation.	Inclusion/Exclusion criteria	No	Yes	Yes
Without concomitant T790M mutation.	Inclusion/Exclusion criteria	No	Yes	Yes
Patients without a M1a stage or M1b or locally advanced disease for which there is curative treatment	Inclusion/Exclusion criteria	No	No	No
ECOG>2	Inclusion/Exclusion criteria	No	No	No
No measurable or evaluable disease (as per RECIST 1.1 criteria). With the exception of pts with asymptomatic and stable brain metastases.	Inclusion/Exclusion criteria	No	Yes	No
Patients without having a pre-dose and a postdose valid result.	Biomarkers	No	No	Yes
Life expectancy <12 weeks.	Inclusion/Exclusion criteria	No	Case by case	No
Adequate organ function	Inclusion/Exclusion criteria	No	Case by case	No
Without capacity of swallow or complete the study.	Inclusion/Exclusion criteria	No	Case by case	No
No relevant toxicities at baseline	Inclusion/Exclusion criteria	No	Case by case	No
Patients who have received prior antineoplastic treatment for advanced disease.	Inclusion/Exclusion criteria	No	Case by case	No
Second active neoplasia	Inclusion/Exclusion criteria	No	Case by case	No

<6 months with prior treatment with cytotoxic chemotherapy for advanced NSCLC.	Inclusion/Exclusion criteria	No	Case by case	No
Patients who have received prior EGFR treatments for lung cancer.	Inclusion/Exclusion criteria	No	Case by case	No
Patients who have received treatment with an investigational drug within 3 weeks before the first day of study treatment.	Inclusion/Exclusion criteria	No	Case by case	No
Treatment with prohibited drugs within 14 days before the first day of study treatment.	Inclusion/Exclusion criteria	No	Case by case	No
Prohibited conocomitant medication	Efficacy and safety	No	Case by case	No
Hypersensitivity to IMP	Investigational Medicinal Product	No	Case by case	No
Serious concomitant systemic disorder, including conditions that could interfere with absortion	Investigational Medicinal Product	No	Case by case	No
IMP overdose	Investigational Medicinal Product	No	Case by case	No
IMP underdose	Investigational Medicinal Product	No	Case by case	No
IMP administration dosing/schedule	Investigational Medicinal Product	No	Case by case	No
IMP toxicity	Investigational Medicinal Product	No	Case by case	No
Tumor assessment not done	Efficacy	No	Yes	No
Tumor assessment out of the window	Efficacy	No	Case by case	No
No baseline tumor assessment	Efficacy	No	Yes	No
No post-baseline tumor assessment	Efficacy	No	Yes	No
Subject not withdrawn as per protocol	Safety	No	Case by case	No