| Clinical Study Protocol | |
|---|---|
| Drug Substance | AZD9291 |
| Study Code | D5160C00042 |
| Version | 3.0 |
| Date | 25 Aug 2017 |

# Detect EGFR T790M mutation in ctDNA of Chinese Advanced/Metastatic NSCLC Patients by Cobas, Super-ARMS, digital PCR and NGS and evaluate clinical outcomes of T790M mutation positive patients who had AZD9291 monotherapy

**Sponsor: AstraZeneca China**

## VERSION HISTORY

**Version 3.0,** 25 Aug 2017

May be applicable for all sites in this study.

Changes to the protocol are summarized below.

Add the following exploratory objectives:

To evaluate concordance, sensitivity, specificity, PPV, NPV of EGFR mutation plasma testing by Bio-rad droplet digital PCR using other plasma tests or tissue test as reference, respectively.

To evaluate the efficacy of patients who receive AZD9291 monotherapy and are T790M mutation positive detected by each of the five platforms, respectively.

Add the "and/or blood" in the exploratory objective: "To explore the mechanisms of acquired resistance in patients who received AZD9291 treatment by NGS testing of tissue and/or blood samples from the collection at PD versus baseline."

In 1.2 Rationale for study design and doses, add "(Thermo Fisher QuantStudio3D digital PCR provided by Novogene Bioinformatics Technology Co. LTD)" after digital PCR in the sentence: "we will compare the Chinese current available methods including Roche Cobas, Super-ARMS (ARMS used in blood test, provided by Amoy Diagnostics Co., Ltd.), digital PCR and Illumina NGS (provided by Guangzhou Burning Rock Medical Examination Institute Co., Ltd.) to obtain descriptive information of each platform and clinically validate the usage of these platforms in companion diagnostic for AZD9291."

In Figure 1 Study flow chart, add note: "QuantStudio3D digital PCR will be used."

In Table 2 Testing Plan, add note: "Samples collected in other treatment visit will also be tested if necessary for exploratory objective."

In 4.1.2 Sample collection, add "QuantStudio3D" before digital PCR in the table and the following sentences:

Remain DNA samples (if any) will be retested by Bio-rad droplet digital PCR platform retrospectively for T790M and sensitizing mutations (if enough amount of samples) and data will be compared with testing results of other four platforms. For retrospective test on all the remain samples, patient who are still on AZD9291 treatment will be informed (or EC approve informed consent waiver); for patient who can't get in touch will apply informed consent waiver. But the investigator should review the medical record to see if the patient expressed any objection to use his/her remain samples for scientific research purpose. If such objection

was recorded, then this patient's remain samples should not be used.

In 4.1.3 Mutation testing & Data management, add the following sentence:

Remain DNA samples (if any) will be retested by Bio-rad droplet digital PCR retrospectively. Testing results and raw data will be transferred from central lab.

In 8.5.3 Exploratory analysis, add the following sentence:

The concordance, sensitivity, specificity, PPV, NPV of EGFR mutation plasma testing by Bio-rad droplet digital PCR using other plasma tests or tissue test as reference will be calculated according to the similar formulas as above. The efficacy of patients who receive AZD9291 monotherapy and are T790M positive patient by each of the five platforms, respectively, will be analyzed same as above.

In 5. STUDY ASSESSMENTS and 8.4 Outcome measures for analyses, add "and sensitizing mutations" after T790M, for instance, "T790M and sensitizing mutations status results and type of test performed. "

In 8.5.4 Analysis timing, add the following: "The exploratory analysis of T790M testing concordance and other testing data at enrollment visit by Bio-rad droplet digital PCR will be conducted once the data is available. "

## PROTOCOL SYNOPSIS

# Detect EGFR T790M mutation in ctDNA of Chinese Advanced/Metastatic NSCLC Patients by Cobas, Super-ARMS, digital PCR and NGS and evaluate clinical outcomes of T790M mutation positive patients who had AZD9291 monotherapy

**National Principal Investigator**

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**Study site(s) and number of subjects planned**

250 patients from the ASTRIS (AccesS to TReatment with AZD9291- International Study) China study during screening will be recruited and 9 hospitals are planned to participate in this testing platforms comparison study.

| **Total planned Study period** | |
|---|---|
| Estimated CSP approved | Q3 2016 |
| Estimated date of first patient in | Q4 2016 |
| Estimated date of last patient in | Q3 2017 |
| Estimated date of last patient last visit | Q1 2019 |
| Estimated date of data base lock | Q2 2019 |
| Estimated date of CSR | Q3 2019 |

**Study design**

This is an open-label, multi-center testing and treatment study in 250 locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) patients with documented epidermal growth factor receptor (EGFR) sensitive mutation and progression (PD) on previous EGFR-TKI. T790M mutation in plasma ctDNA will be tested by four methods including Roche Cobas, Super-ARMS, digital PCR and NGS in order to compare the detection methodology and clinical outcomes of T790M mutation positive (by any one of the four platforms) patients who receive AZD9291 monotherapy in ASTRIS study will be evaluated and combined with the testing results.

**Objectives**

| **Primary Objectives:** | **Outcome Measure:** |
|---|---|
| To evaluate concordance of T790M mutation plasma testing between the Cobas test and each of other platforms: Super-ARMS, digital PCR or NGS. | Concordance |
| To assess the efficacy of AZD9291 monotherapy by assessment of PFS in adult patients with advanced or metastatic NSCLC, who have received prior EGFR-tyrosine kinase inhibitor (TKI) therapy and are T790M mutation positive detected by any one of the four plasma testing platforms: Cobas/Super-ARMS/ digital PCR/NGS. | Progression-free survival (PFS) using investigator assessments according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) |
| **Secondary Objective:** | **Outcome Measure :** |
| To evaluate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of Super-ARMS/digital PCR/NGS by using Cobas as the reference. | Testing sensitivity, specificity, PPV, NPV |
| To assess the efficacy of AZD9291 monotherapy by assessment of overall response rate (ORR) and overall survival (OS) in adult patients with advanced or metastatic NSCLC, who have received prior EGFR-TKI therapy and are EGFR T790M mutation positive detected by any one of the four plasma testing platforms: Cobas/Super-ARMS/ digitial PCR/NGS. | Overall response rate (ORR), overall survival (OS) |
| **Exploratory objectives:** | **Outcome Measure:** |
| To dynamically monitor EGFR mutations by NGS and digital PCR in ctDNA of patients receiving AZD9291 treatment. | Proportion of patients with each EGFR mutation (C797S and T790M etc.) at different time point. |
| To explore the mechanisms of acquired resistance in patients who received AZD9291 treatment by NGS testing of tissue and/or blood samples from the collection at PD versus baseline. | Changes of distribution of resistance related genes at PD compared with baseline. |
| To describe the genomic profile of long-term survivors, especially to find out potential genomic prognosis and/or predictive factors for AZD9291 long-term efficacy as compared to rapid PD patients. | Key genetic and proteomic markers including, but not limited to, EGFR mutations |
| To evaluate concordance, sensitivity, specificity, PPV, NPV of EGFR mutation plasma testing by Bio-rad droplet digital PCR using other plasma test or tissue test as reference, respectively. | Testing concordance, sensitivity, specificity, PPV, NPV |
| To evaluate the efficacy of patients who receive AZD9291 monotherapy and are T790M mutation positive detected by each of the five platforms, respectively. | ORR, PFS, OS |

**Target subject population**

250 locally advanced or metastatic EGFR mutation positive NSCLC patients with progression on a previous EGFR-TKI will be recruited.

**Investigational product, dosage and mode of administration**

AZD9291 is an oral, potent, selective, irreversible inhibitor of both EGFR-TKI sensitizing and resistance mutations in NSCLC with a significant selectivity margin over wild-type EGFR. Patient who is positive in plasma T790M mutation test by any one of the four platforms and meet the eligibility criteria for treatment will receive AZD9291 monotherapy in ASTRIS study.

AZD9291 will be administered orally as one 80 mg tablet once a day.

**Duration of treatment**

Patients may continue to receive AZD9291 as long as they continue to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria (see section 3.11). The study will be closed in a maximum period of 18 months after the last patient is enrolled. Contingencies will be made to ensure continued drug supply for patients who are still deriving benefit from AZD9291 at that time.

**Statistical methods**

The concordance of T790M resistance mutation testing between the Cobas test and each of other platforms will be calculated. The sensitivity, specificity, PPV and NPV of each testing platform (Super-ARMS, digital PCR, and NGS) will be calculated with the Cobas test as the reference. The Kappa coefficient will be calculated to measure the agreement of T790M mutation testing between the Cobas test and each of other platforms. Descriptive statistics will be provided for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, interquartile range (Q1, Q3), minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. The 95% confidence interval (CI) will be calculated as appropriate. PFS and OS, respectively, will be summarized using Kaplan-Meier estimates of the median time to event (progression and death) and quartiles together with their 95% confidence intervals.

The chi-square test will be used to compare the sensitivity, specificity, and concordance between any of the two platforms using Cobas as reference testing in an exploratory manner.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

| Abbreviation or special term | Explanation |
|---|---|
| ASTRIS | AccesS to TReatment with AZD9291- International Study |
| AE | Adverse Event |
| ADR | Adverse Drug Reaction |
| ALK | Anaplastic lymphoma kinase |
| ALT | Alanine aminotransferase |
| ARMS | Amplification Refractory Mutation System |
| AZ | AstraZeneca |
| aNSCLC | advanced Non-small Cell Lung Cancer |
| BCRP | Breast Cancer Resistance Protein |
| CI | Confidence Interval |
| CRF | Case Report Form (electronic/paper) |
| CRO | Clinical Research Organisation |
| CSA | Clinical Study Agreement |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CT | Computer tomography |
| CTCAE | Common Terminology Criteria for Adverse Event |
| ctDNA | Circulating Tumor DNA |
| cfDNA | Cell Free DNA |
| CYP | Cytochrome P450 |
| Digital PCR | Droplet Digital Polymerase Chain Reaction |
| DLT | Dose limiting toxicity |
| DMC | Data Monitoring Committee |
| DNA | Deoxyribonucleic acid |
| DoR | Duration of Response |
| EC | Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC) |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |

| Abbreviation or special term | Explanation |
|---|---|
| EDC | Electronic Data Capture |
| EGFR | Epidermal Growth Factor Receptor |
| EGFRm+ | Epidermal Growth Factor Receptor mutation positive |
| EGFR-TKI | Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor |
| FFPE | Formalin-Fixed, Paraffin-Embedded |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| IB | Investigator's Brochure |
| ILD | Interstitial lung disease |
| ICH | International Conference on Harmonisation |
| IP | Investigational Product |
| IRB | Independent Review Board |
| IUS | Intra uterine System |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| LSLV | Last Subject Last Visit |
| NGS | Next Generation Sequence |
| NPV | Negative predictive value |
| NSCLC | Non-small Cell Lung Cancer |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PD | Progression of disease |
| PPV | Positive predictive value |
| PFS | Progression Free Survival |
| PK | Pharmacokinetics |
| qPCR | Quantitative Polymerase Chain Reaction |
| QT | Interval on the electrocardiogram representing the duration of depolarization and repolarization of the heart |
| QTc | The QT interval corrected for heart rate |
| RECIST v1.1 | Response Evaluation Criteria in Solid Tumors version 1.1 |

| Abbreviation or special term | Explanation |
|---|---|
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| T790M | An amino acid substitution at position 790 in EGFR, from a Threonine (T) to a Methionine (M) |
| TKI | Tyrosine kinase inhibitor |
| ULN | Upper limit of normal |
| Variable | A characteristic of a property of a subject that may vary e.g., from time to time or between subjects |
| WHO | World Health Organization |

# INTRODUCTION

## 1.1 Background and rationale for conducting this study

Somatic mutations in EGFR are detected approximately 30 to 40% of NSCLCs from Asian patients (Lynch et al., 2004; Paez et al., 2004; Shigematsu et al., 2005). EGFR-TKI has opened a new paradigm for the treatment of advanced NSCLC (aNSCLC). Several studies have shown that EGFR-TKI significantly improves PFS (Progression-Free Survival) and ORR (Objective response rate) compared with platinum-doublets in the first line treatment for aNSCLC harbouring activating EGFR mutations (Maemondo et al., 2010; Rosell et al., 2012; Sequist et al., 2013).

However, patients ultimately develop acquired resistance to these agents with progression of disease after approximately 9 to 13 months (Engelman and Janne, 2008; Mok et al., 2009; Pao et al., 2005; Rosell et al., 2012). In approximately 60% of these patients, the mechanism of acquired resistance is the development of an additional EGFR mutation, EGFR T790M(Yu et al., 2013). One strategy to overcome this mechanism of resistance is through the use of irreversible EGFR inhibitors for second-line treatment (Kobayashi et al., 2005). Osimertinib (TAGRISSO, AZD9291) is a highly selective, irreversible 3$^{rd}$ generation of EGFR-TKI that targets both EGFR-TKI-sensitizing mutations (e.g., exon 19 deletion and L858R) and the T790M resistance mutation (Cross et al., 2014). Oral presentations about AZD9291 from AURA studies in 2016 ELCC showed that AZD9291 80 mg QD as first-line treatment for EGFR active mutation (mPFS 19.3m) aNSCLC patients and for pre-treated EGFR-TKI aNSCLC patients harbouring T790M-positive mutation are safe and effective (mPFS 9.7-11.0m). In patients with NSCLC, especially who initially respond to EGFR-TKI therapy develop resistance, it is now recommended to obtain a biopsy in order to characterize the mechanism of resistance. However, in clinical practice, tumour tissue testing, in general, faces two challenges: specimens with limited tumour cells and tissue heterogeneity. Obtaining sufficient tissue for mutation analysis in patients with advanced disease is challenging, as invasive interventions may be ineffective and unsafe. Moreover, detection of disease-relevant mutations from the biopsy of a single tumor lesion may not be reflective of the patient's complete disease burden, especially in heterogeneous cancers (Fisher et al., 2013; Weber et al., 2014). Therefore, molecular assays that detect secondary mutations without repeat invasive tissue biopsies are needed.

In recent years, circulating tumor DNA (ctDNA) has emerged as a specific and sensitive blood-based biomarker for detection of EGFR mutations. Several studies have demonstrated

that mutations, including the EGFR T790M mutation, detected in plasma ctDNA are highly concordant with those detected in tumor tissue in patients (Douillard et al., 2014a; Douillard et al., 2014b; Gevensleben et al., 2013; Punnoose et al., 2012). A new study shows that plasma EGFR T790M ctDNA status is associated with clinical outcome in aNSCLC patients with acquired EGFR-TKI resistance(Zheng et al., 2016), indicating that ctDNA as a liquid biopsy is a feasible and minimally invasive alternative to tissue biopsy. In addition, because ctDNA analysis does not involve formaldehyde fixation, there is reduced frequency of a false positive result due to deamination (Denis et al., 2015). In general, plasma ctDNA testing has the potential to rapidly identify NSCLC patients suitable for targeted therapy and availability of these simple blood tests may streamline diagnosis, including for patients where tumor samples are unavailable. Therefore, sensitive, specific, reliable and fast mutation analysis platforms for plasma are needed in diagnosis of EGFR T790M for AZD9291 clinical development program including testing the acquired C797S mutation upon treatment with AZD9291 (Song et al., 2016).

There are several methodologies available for mutation analysis using ctDNA. However, since ctDNA often represents a small fraction (<1.0%) of total cfDNA (cell-free DNA), its detection remains challenging (Diaz and Bardelli, 2014) and the sensitivity is still an issue in various platforms. Direct sequencing approaches like Sanger sequencing or pyrosequencing are not suitable for detecting EGFR mutations using ctDNA on this account. Several different types of PCR-based assays have been explored for ctDNA genotyping including non-digital platforms and digital platforms. Non-digital PCR mainly include Roche Cobas and amplification-refractory mutation system (ARMS). Roche Cobas ® EGFR Mutation Test is the approved companion diagnostic for AZD9291. ARMS, also known as allele-specific polymerase chain reaction (ASPCR), is a reliable method for detecting single base mutations or small deletions which is based on the use of sequence-specific PCR primers (Newton et al., 1989). Because Taq DNA polymerase is effective at distinguishing between a match and a mismatch at the 3’ end of a primer, specific mutated sequences are selectively amplified. Specific ARMS primers have been designed and optimized for detecting various EGFR mutations and have been widely used for ctDNA based assays.

Digital platform mainly refers to digital polymerase chain reaction (digital PCR), which is a refinement of conventional PCR that can be used to directly quantify and clonally amplify nucleic acids (Pohl and Shih, 2004; Vogelstein and Kinzler, 1999). Digital PCR is widely used for many clinical applications in China due to its unparalleled sensitivity and precision. It is to amplify a single DNA template from minimally diluted samples and generate amplicons that are exclusively derived from one template. These amplicons can be detected with different

fluorophores or sequenced to distinguish different alleles. Thus, digital PCR transforms the exponential, analog nature of the conventional PCR into a linear, digital signal, suitable for statistical analysis. Digital PCR has been applied in quantification of EGFR mutants in clinical specimens, especially in dynamic monitoring of patients for the development of resistance mutations, providing a promising molecular diagnostic tool (Yung et al., 2009).

The ability of Cobas, ARMS and digital PCR to detect EGFR mutations, including T790M, from ctDNA in aNSCLC was compared using a small number of samples in countries outside of China. For the T790M mutation, the digital platforms outperformed the non-digital platforms, and the Cobas® EGFR Mutation Test and BEAMing digital PCR demonstrated a high sensitivity for T790M (Thress et al., 2015). The feasibility of digital PCR was demonstrated in a recent study in monitoring EGFR mutation dynamics in serial plasma samples from NSCLC patients receiving TKI therapy and T790M can be detected in plasma ctDNA before and after PD as a poor prognostic factor (Zheng et al., 2016).

In addition, next generation sequencing (NGS) has also been used in EGFR mutation testing in ctDNA, although there are also practical challenges to a successful implementation of NGS technologies for China clinical applications. In summary, a number of technologies have entered the market of T790M detection, with several types of equipment based on different molecular biological principles.

To date, the Cobas® EGFR Mutation Test will be used to test the T790M resistance mutation in EGFR-TKI resistant patients in China for ASTRIS patient recruitment . Meanwhile alternative strategies are also being evaluated, namely EGFR mutation testing using plasma ctDNA. To this end, a comparison of multiple platforms for the detection of EGFR mutations in plasma ctDNA to identify technology that is more appropriate for use during AZD9291 clinical development is needed.

## 1.2 Rationale for study design and doses

Accurate identification of NSCLC patients carrying key molecular mutations is essential for delivering AZD9291 targeted therapies to those most likely to benefit. Detection of plasma ctDNA in a simple blood test offers a minimally invasive alternative to tumor tissue biopsy, and is already available for identifying patients suitable for treatment with Iressa. As reported in a recent study, the clinical response rate (ORR) and median PFS of AZD9291 monotherapy were similar in patients with T790M-positive plasma (ORR, 63%; PFS, 9.7 months) or T790M-positive tumor (ORR, 62%; PFS, 9.7 months) results (Oxnard et al., 2016). Because

different technology platforms data for T790M detection in blood is insufficient in China, we will compare the Chinese current available methods including Roche Cobas, Super-ARMS ( ARMS used in blood test, provided by Amoy Diagnostics Co., Ltd.), digital PCR(Thermo Fisher QuantStudio3D digital PCR provided by Novogene Bioinformatics Technology Co. LTD) and Illumina NGS (provided by Guangzhou Burning Rock Medical Examination Institute Co., Ltd.) to obtain descriptive information of each platform and clinically validate the usage of these platforms in companion diagnostic for AZD9291. We hope to deliver the right treatment to the right patient based on scientific research, with updates from this pioneering plasma ctDNA trial.

In addition, the potential to accurately quantify EGFR mutations in plasma from NSCLC patients would enable more rapid and more frequent analyses to assess disease status; however, the utility of such analyses for clinical purposes has only recently started to explore in China. In this study, we will try to use digital PCR and NGS to monitor EGFR mutations (C797S, reported acquired resistance to the 3rd generation of EGFR-TKIs, and T790M etc.) dynamics in serial plasma samples from NSCLC patients during AZD9291 treatment and get data about clinical response with relevant implications for patient management. We will also explore the acquired resistance to the 3rd generation of EGFR-TKIs by NGS testing of tissue samples from the collection at PD to compare with baseline and to investigate biomarker characteristics of long-term survival patients under AZD9291 treatment.

### Rationale for doses

The selected AZD9291 starting dose of 80 mg is the recommended phase II dose , and the same dose of 80 mg AZD9291 is used in the phase III registration study. This is not the maximum tolerated dose (MTD) as AZD9291 was administered up to 240 mg daily with no dose-limiting toxicity (DLT) observed.

## 1.3 Benefit/risk and ethical assessment

In this study, a minimally invasive alternative to tissue sample in diagnosis of T790M mutation will be used, namely plasma ctDNA will be tested by four methods (Roche Cobas, Super-ARMS, digital PCR and NGS), and patients with positive T790M mutation confirmed by any one of the platforms will receive AZD9291 treatment in ASTRIS studyif meet the eligibility criteria for treatment. Roche Cobas plasma test has already been approved as companion diagnostic for AZD9291, although the other three testing methods in plasma has not been approved yet. The key efficacy and safety findings from the clinical programme of AZD9291 are summarised below:

- Patients with tumors harboring the T790M appeared to have improved responses (ORRs in these patients ranged from 66% to 71%) compared with responses in patients with tumors without the presence of T790M. The median duration of response

calculated as 9.6~12.5 months and the median PFS was 9.7~11.0 months for the 80 mg dose in patients with tumors harboring the T790M. (data cut-off date January 2016, 2016ELCC).

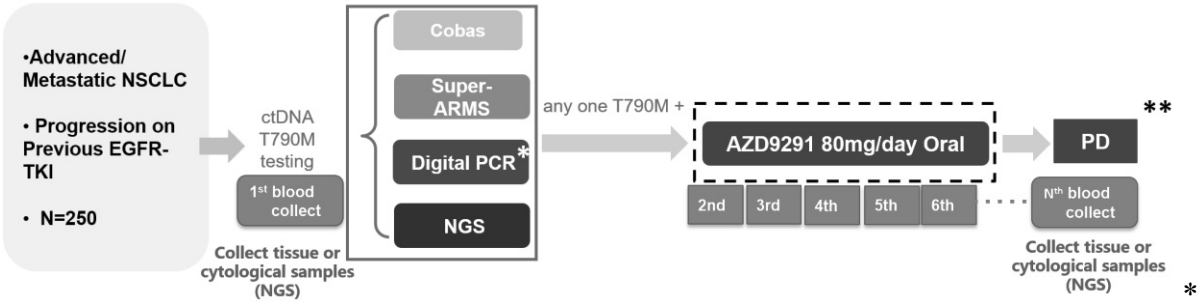
- The clinical response rate (ORR) and median PFS were similar in patients with T790M-positive plasma (ORR, 63%; PFS, 9.7 months) or T790M-positive tumor (ORR, 62%; PFS, 9.7 months) results(Oxnard et al., 2016).
- The most commonly reported adverse events (AEs) were rash, diarrhoea, paronychia and dry skin. The most common SAEs by System Organ Class (SOC) were respiratory, thoracic and mediastinal disorders, gastrointestinal disorders, metabolism and nutrition disorders, and blood and lymphatic system disorders.

Given the clinical activity noted to date with AZD9291, the acceptable safety profile demonstrated thus far, and the inclusion/exclusion criteria of treatment period stipulated in this study protocol, it is reasonable and appropriate to make AZD9291 available to patients with T790M positive (by plasma testing) NSCLC that no longer responding to previous EGFR-TKI.

## 1.4 Study Design

This is an open-label, multi-center testing and treatment study in 250 locally advanced or metastatic NSCLC patients with documented EGFR sensitive mutation and progression on previous EGFR-TKI. T790M mutation in plasma ctDNA will be tested by four methods including Roche Cobas, Super-ARMS, digital PCR and NGS in order to evaluate the concordance of T790M testing in plasma between the Cobas test and each of other platforms as one of the primary endpoint.
Patients who are T790M mutation positive in plasma test by any one of the four platforms and meet the eligibility criteria of treatment period will receive AZD9291 treatment in ASTRIS study. The other primary endpoint for this study is PFS (defined by RECIST v1.1), as assessed by the Investigator. Patients may continue to receive AZD9291 as long as they continue to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria (see section 3.11). The sponsor will be assessing OS and ORR as a secondary endpoint.

**Figure 1 Study flow chart**




QuantStudio3D digital PCR will be used. **Patients will be followed for progression and survival.

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

| Primary Objectives: | Outcome Measure: |
|---|---|
| To evaluate concordance of T790M plasma mutation testing between the Cobas test and each of other platforms: Super-ARMS, digital PCR or NGS. | Concordance |
| To assess the efficacy of AZD9291 monotherapy by assessment of PFS in adult patients with advanced or metastatic NSCLC, who have received prior EGFR- TKI therapy and are T790M mutation positive detected by any one of the four plasma testing platforms: Cobas/Super-ARMS/ digital PCR/NGS. | PFS using investigator assessments according to RECIST v1.1 |

### 2.2 Secondary objectives

| Secondary Objective: | Outcome Measure : |
|---|---|
| To evaluate the sensitivity, specificity, PPV and NPV of Super-ARMS/digital PCR/NGS by using Cobas as the reference. | Testing sensitivity, specificity, PPV, NPV |
| To assess the efficacy of AZD9291 monotherapy by assessment of ORR and OS in adult patients with advanced or metastatic NSCLC, who have received prior EGFR-TKI therapy and are T790M mutation positive detected by any one of the four plasma testing platforms: Cobas/Super-ARMS/ digital PCR/NGS. | ORR, OS |

## 2.3 Safety objectives

N/A

### 2.4 Exploratory objectives

| Exploratory objectives: | Outcome Measure : |
|---|---|
| To dynamically monitor EGFR mutations by NGS and digital PCR in ctDNA of patients receiving AZD9291 treatment. | Proportion of patients with each EGFR mutation (C797S and T790M etc.) at different time point. |
| To explore the mechanisms of acquired resistance in patients who received AZD9291 treatment by NGS testing of tissue and/or blood samples from the collection at PD versus baseline. | Changes of distribution of resistance related genes at PD compared with baseline. |

| | |
|---|---|
| To describe the genomic profile of long-term survivors, especially to find out potential genomic prognosis and/or predictive factors for AZD9291 long-term efficacy as compared to rapid PD patients. | Key genetic and proteomic markers including, but not limited to, EGFR mutations |
| To evaluate concordance, sensitivity, specificity, PPV, NPV of EGFR mutation plasma testing by Bio-rad droplet digital PCR using other plasma test or tissue test as reference, respectively. | Testing concordance, sensitivity, specificity, PPV, NPV |
| To evaluate the efficacy of patients who receive AZD9291 monotherapy and are T790M mutation positive detected by each of the five platforms, respectively. | ORR, PFS, OS |

# 3. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

## 3.1 Inclusion criteria for testing period

For inclusion in the study subjects should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures.

2. Adults (according to China regulations for age of majority)

3. Histological or cytological confirmed locally advanced NSCLC (stage IIIB) or metastatic (stage IV) NSCLC, not amenable to curative surgery or radiotherapy.

4. Patients who have progressed following prior therapy with an EGFR-TKI agent.

## 3.2 Exclusion criteria for testing period

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Patients who disagree to participate this study.

2. Patients whose medical objection was recorded to use the existing data from medical practice for scientific research.

## 3.3 Inclusion criteria for treatment period

The study subjects must fulfil the following criteria for entry to treatment period:

1. Documented EGFR mutation positive (at any time since the initial diagnosis of NSCLC) known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q).
2. Confirmed T790M mutation positive in plasma by any one of the four platforms (Cobas, Super-ARMS, digital PCR and NGS)
3. World Health Organization (WHO) performance status 0-2.
4. Adequate bone marrow reserve and organ function as demonstrated by complete blood count, biochemistry in blood and urine at baseline.
5. ECG recording at baseline showing absence of any cardiac abnormality as per exclusion criterion #6.
6. Females should be using adequate contraceptive measures, should not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria:
    a. Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments
    b. Women under 50 years would be consider post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution
    c. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
7. Male patients must be willing to use barrier contraception. (see Restrictions, Section 3.10)
8. At least one lesion, not previously irradiated and not chosen for biopsy during the study Screening period, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis of ≥15 mm) with computerized tomography (CT), and which is suitable for accurate repeated measurements.

## 3.4 Exclusion criteria for treatment period

Patients will not entry to treatment period in this study if any of the following exclusion criteria are met:

1. Previous (within 6 months) or current treatment with AZD9291.

2. Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of AZD9291) any treatment known to be potent inhibitors or inducers of cytochrome P450 (CYP) 3A4 (Appendix C)

3. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, active infection including hepatitis B, hepatitis C and human immunodeficiency virus, or significantly impaired bone marrow reserve or organ function, including hepatic and renal impairment, which in the investigator's opinion would significantly alter the risk/benefit balance.

4. Patient with symptomatic central nervous system (CNS) metastases who is neurologically unstable or has required increasing doses of steroids to manage CNS symptoms within the 2 weeks prior to start AZD9291 administration

5. Past medical history of ILD, drug-induced ILD, radiation pneumonitis requiring steroid treatment, or any evidence of clinically active ILD

6. Any of the following cardiac criteria:

    a. Mean resting corrected QT interval (QTcF) > 470 ms using Fredericia's formula :

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

    b. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block)

    c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events

7. Any unresolved toxicity from prior therapy CTCAE $\geq$ grade 3 at the time of starting treatment

8. History of hypersensitivity to excipients of AZD9291 or to drugs with a similar chemical structure or class to AZD9291

9. Women who are breast-feeding

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.6.

## 3.5 Subject enrolment

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject or their guardian/legal representative before any study specific procedures are performed.

2. Each patient will use a unique identifier assigned through the Interactive Voice Response System (IVRS)/ Interactive Web Response System (IWRS) of ASTRIS study in the following format SCCNN**3**XX: CC being the country code, NN being the centre number and 3XX being the subject enrolment code at the centre into the study.

3. Determine subject eligibility. See Section 3.1&3.2.

4. Collect blood samples from patients enrolled in this study. Tumor tissue is also recommended to be collected optionally (or cytological samples, pleural fluid etc., if tissue is not available) per the judgement of treating physician.

## 3.6 Procedures for handling incorrectly enrolled subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria for treatment period must not be initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

## 3.7 Methods for assigning treatment groups

Patient who is positive in plasma T790M mutation test by any one of the four platforms and meet the eligibility criteria (see section 3.3 & 3.4) for treatment period will receive AZD9291 treatment and be followed. If Subject negative for T790M mutation in plasma by all four platforms is T790M positive in tissue and then receives AZD9291 monotherapy, the subject will have RECISTv1.1 assessment every 6 weeks (provided with free CT scan) and be followed for OS and data will be collected. Patient negative for T790M mutation both in plasma by all four platforms and in tissue will not be followed in this study.

## 3.8 Methods for ensuring blinding

Not applicable.

## 3.9 Methods for unblinding

Not applicable.

## 3.10 Restrictions

The following restrictions apply while the patient is receiving AZD9291 and for the specified times before and after:

1. Female of child-bearing potential should use reliable methods of contraception from the time of screening until 6 weeks after discontinuing study treatment. Acceptable methods of contraception include total sexual abstinence, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions [IUS Levonorgestrel Intra Uterine System (Mirena), Medroxyprogesterone injections (Depo-Provera)], copper-banded intra-uterine devices and vasectomised partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse.

2. Male patients should be asked to use barrier contraceptives (i.e., by use of condoms) during sex with all partners during the trial and for a washout period of 4 months. Patients should avoid procreation for 6 months after completion of trial treatment. Patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

3. If medically feasible, patients taking regular medication, with the exception of potent inhibitors or inducers of CYP3A4 (see Appendix C to), should be maintained on it throughout the study period (30 days post-last dose). Patients taking concomitant medications whose disposition is dependent upon CYP3A4 and breast cancer resistance protein and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving AZD9291. Patients taking concomitant medications whose disposition is dependent upon CYP3A4, CYP1A2, CYP2C or p-glycoprotein and which have a narrow therapeutic index should be closely monitored for reduction in therapeutic activity as a result of the reduced exposure of the concomitant medication while receiving AZD9291. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Appendix C).

   Up to 3-fold increase in exposure may occur in statin exposure when coadministered with AZD9291. It is recommended that the starting and maintenance dose of statins should be as low as possible and should be guided by the statin prescribing information.

   Patients taking warfarin should be monitored regularly for changes in prothrombin time or international normalized ratio.

4. Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE grade $\leq$2) while receiving treatment with AZD9291 until at least one week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade $\geq$3) ocular events, they must discontinue wearing their contact lenses until at least one week after treatment with AZD9291 is permanently discontinued. Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed to by a study doctor, at any time

during the study until 1 week after AZD9291 has been permanently discontinued. Patients must consult their investigator promptly if they have any concerns.

## 3.11 Discontinuation of investigational product

Subjects may be discontinued from AZD9291 treatment in the following situations:

- The investigator thinks that it is in the patient's best interest to stop therapy
- Patient decision: the patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Confirmed diagnosis of ILD
- Ulcerative ocular events
- Other manifestation of unacceptable toxicity
- Pregnancy
- Patient incorrectly enrolled or treated on the study
- Patient starts receiving additional anti-cancer therapy
- Lost to follow up (unsuccessful contact with patient despite every effort made by investigator)
- Termination of the study (see Sections 3.13 & 10.2.4)

The patient or representative (e.g. caregiver, family member) must return all unused investigational product (IP).

### 3.11.1 Procedures for discontinuation of a subject from investigational product

All reasons for discontinuation of treatment must be documented. Any subject who discontinues study treatment for reasons other than objective disease progression should have tumour assessments performed as scheduled in the protocol (serial plasma collection not required) until disease progression is documented or death occurs, unless consent is withdrawn.

If a subject is withdrawn from study, see Section 3.12.

## 3.12 Criteria for withdrawal

Patients are free to discontinue AZD9291 treatment or withdraw from the study without prejudice to further treatment.

Reasons for withdrawal from the study:

- Eligibility criteria not fulfilled
- Death
- Lost to follow up
- Withdrawal of consent.

If a subject wishes to withdraw their consent to this study, it must be clear if the subject agrees to store their samples or destroy the remaining specimen (see section 5.7 for detail information on biological sample handling).

If a subject wishes to withdraw their consent to both treatment and study assessments, they should be asked if they are willing to continue with survival follow-up (which can be conducted by telephone). If a subject wishes to withdraw their consent to further participation in the study entirely, including survival follow-up, this should be clearly documented in the subject notes and in the CRF.

The status of ongoing, withdrawn (from the study) and "lost to follow-up" subjects at the time of an overall survival analysis should be obtained by the site personnel by checking the subjects notes, hospital records, contacting the subjects general practitioner and checking publicly available death registries. In the event that the subject has actively withdrawn consent to the processing of their personal data, the vital status of the subject can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

The withdrawal reasons must be documented and SAEs reported appropriately in the CRF. If the patient agrees, the investigator must follow the patient for safety reasons until 30 days post-last dose, and then for survival status (and also for progression status if the subject had not progressed). If patient declines, the investigator will separately follow up and manage any SAEs as a matter of clinical practice. The patient or representative will return unused AZD9291 tablets.

## 3.13 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

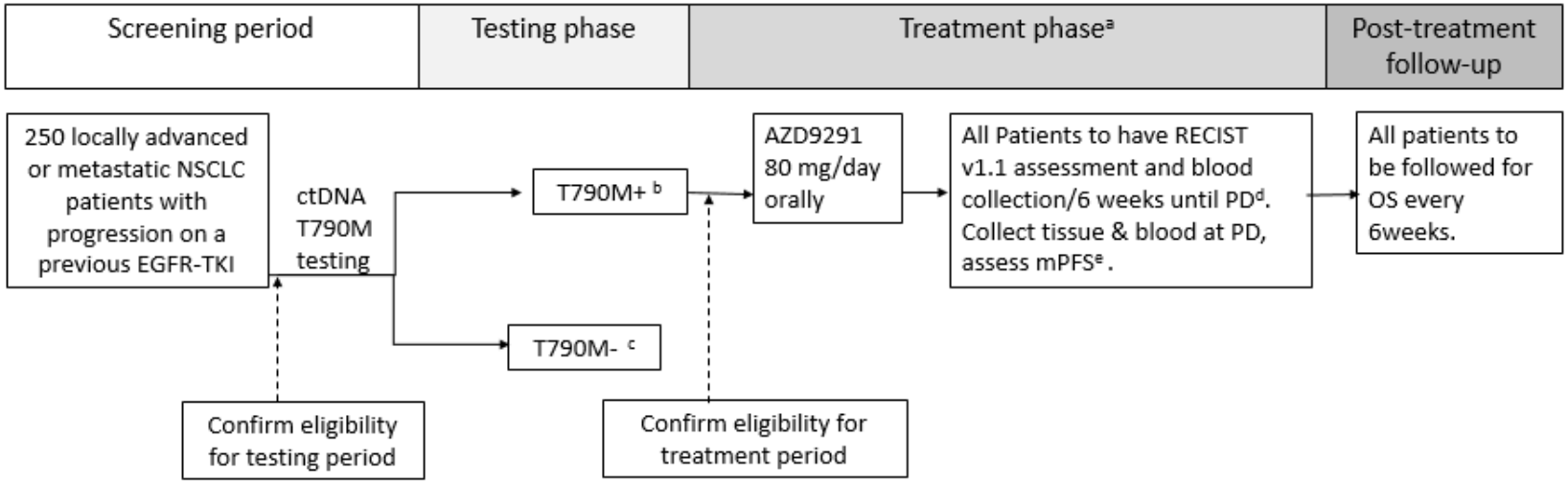
- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Patients withdrawing from the treatment prior to study closure will be followed up as part of this study. Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF.

In terminating the study, AstraZeneca will ensure that adequate consideration is given to the protection of the subjects' interests.

# 4. STUDY PLAN AND TIMING OF PROCEDURES

Figure 2 Study Plan




EGFR-TKI = EGFR Tyrosine Kinase Inhibitor; NSCLC = Non-small Cell Lung Cancer; PFS=progression free survival; ORR= overall response rate; OS = overall survival; PD = disease progression; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1

a Patients will continue to receive study drug until objective disease progression or as long as they are continuing to show clinical benefit, as judged by the investigator.

b Patient with T790M mutation positive in plasma test by any one of the four platforms will be checked for inclusion/exclusion criteria for treatment period. Only subjects who meet all of the inclusion criteria and none of the exclusion criteria will initiate treatment with AZD9291.

c If Subject negative for T790M mutation in plasma by all four platforms is T790M positive in tissue and then receives AZD9291 monotherapy, the subject will have RECISTv1.1 assessment every 6 weeks (provided with free CT scan) and be followed for OS and data will be collected.

d Patients who discontinue treatment prior to PD will continue to have tumor assessment every 6 weeks (serial blood collection not required) until objective progression or death occurs, unless consent is withdrawn.

e Patients who continue treatment after objective progression due to clinical benefit will be followed up as per standard practice post progression, and blood will be collected at 1st visit post-PD.

Table 1 Study Plan

| | **Screening/ Enrolment visit** | | **Treatment visit** | | **Treatment Discontinuation** | **30 day follow-up[f]** | **Progression Follow-up** | **Survival visit** |
|---|---|---|---|---|---|---|---|---|
| | -28 days | | Day 1 | **(every 6 weeks)** | | | **(every 6 weeks)** | **(every 6 weeks)** |
| **Windows (days)** | | | | +/- 7 days | +/- 7 days | +/- 7 days | +/- 7 days | +/- 7 days |
| Informed Consent | X | | | | | | | |
| Inclusion/Exclusion criteria (for testing period) check | X | | | | | | | |
| Complete enrolment form | X | | | | | | | |
| Patient demographics | X | | | | | | | |
| Smoking history | X | | | | | | | |
| Medical history | X | | | | | | | |
| Disease characteristics | X | | | | | | | |
| Cancer treatment history | X | | | | | | | |
| Collect tumor tissue samples or or cytological samples like pleural fluid. [a] | X | | | If radiographic progression observed, collect tissue | | | | |
| Collect blood sample | X | | | X[b] | | | | |
| EGFR T790M status confirm | X | | | | | | | |
| WHO Performance status | X | X | | X | X | | | |
| Inclusion/Exclusion criteria (for treatment period) check | | X | | | | | | |
| Plasma AZD9291 testing[c] | | X | | | | | | |
| Concomitant medications | | X | X | X | X | | | |
| Complete blood count | | X | | If clinically indicated or per institutional standard of care | If clinically indicated or per institutional standard of care | | | |
| Biochemistry in blood and urine | | X | | If clinically indicated or per institutional standard of care | If clinically indicated or per institutional standard of care | | | |
| Pregnancy test[d] | | X | | | | | | |

| | Screening/ Enrolment visit | | Treatment visit | | Treatment Discontinuation | 30 day follow-up[f] | Progression Follow-up | Survival visit |
|---|---|---|---|---|---|---|---|---|
| Physical examination | | X | | | X | | | |
| Weight | | X | | X | X | | | |
| ECG recording | | X | | If clinically indicated or per institutional standard of care | If clinically indicated or per institutional standard of care | | | |
| Visual test (slit-lamp) | | X | | If clinically indicated or per institutional standard of care | If clinically indicated or per institutional standard of care | | | |
| Dispense AZD9291 (IVRS/IWRS) | | | X AZD9291 start-dose | X AZD9291 re-supply | | | | |
| AZD9291 dosing (daily):<br>- current dose; dose adjustment; interruption/discontinuation reason for change | | | | X | | | | |
| Drug accountability | | | | X | | | | |
| Tumor assessment (RECIST v1.1) | | X | | X | X[e] | | X[e] | |
| AE/SAE report[f] | | X | X | X | X | X | X | |
| Reason for withdrawal | | | | | X | | | |
| Survival status | | | | | | | | X |

(a) Samples will be collected at enrolment visit and at disease progression, then tested by NGS retrospectively in patients who received AZD9291 treatment to explore the resistance mechanisms.

(b) For dynamic monitoring, the peripheral blood will be collected every 6 weeks during the AZD9291 treatment, at radiographic progression and at 1st visit post-PD (if patient continue to receive AZD9291 treatment as judged by the investigator).

(c) Before initiating treatment, the pre-dose plasma samples of T790M mutation positive patients will undergo bio-analysis testing for detecting AZD9291 for screening purpose according to validated testing procedures. If AZD9291 are detected in the samples, patient will not receive treatment.

(d) Pregnancy test (pre-menopausal female patients only) to be performed in accordance with local standards.

(e) Patients who discontinue treatment prior to PD will continue to have efficacy assessment every 6 weeks (serial blood collection not required) until objective progression or death occurs, unless consent is withdrawn.

(f) All AEs/SAEs has reported in ASTRIS main study should not be reported repeatedly in current study. A 30 day post last dose follow up assessment will required if on treatment-assessment was abnormal at treatment discontinuation.

**Table 2 Testing Plan**

| | **Screening/ Enrolment period** | **Treatment period (treatment visit every 6 weeks)** | | | | | |
|---|---|---|---|---|---|---|---|
| **Testing Windows (days)** | -28 days | Day 1 | First after treatment (6w) | Best response | 6w before radiographic progression (optional) | Radiographic progression | 6w after radiographic progression (optional) |
| Dynamic monitoring using serial plasma samples by NGS (168 genes) and digital PCR* | X | | X | X | X | X | X |
| Tissue or cytological samples NGS test (295 genes) | X (recommended option) | | | | | X (recommended option) | |

*Samples collected in other treatment visit will also be tested if necessary for exploratory objective.

## 4.1 Enrolment/screening period

Procedures will be performed according to the Study Plan.

At screening, consenting subjects are assessed to ensure that they meet eligibility criteria for testing period. Subjects who do not meet these criteria must not be enrolled in the study.

The investigator will inform the patients about the study, AZD9291, the potential benefits and risks, AE reporting, as well as other information collected within the scope of the study. Subsequently, the investigator will obtain signed informed consent from the potential patient or legally acceptable representative, as appropriate per local regulations.

All subjects will be required to provide consent to supply tissue and blood samples for entry into this study. This consent is included in the main subject informed consent form.

Each patient will use a unique identifier assigned through the Interactive Voice Response System (IVRS)/ Interactive Web Response System (IWRS) of ASTRIS study in the following format SCCNN**3**XX: CC being the country code, NN being the centre number and 3XX being the subject enrolment code at the centre into the study.

### 4.1.1 Data collections

Collected clinical information will include patient demographics (gender, age), Smoking history (non-smoker, ex-smoker and current smoker according to the status before AZD9291 treatment), disease characteristics like clinical TNM staging, medical history, cancer treatment history, WHO Performance status, etc. Collected molecular diagnosis information will include detection platform, date of sampling & submission & examining report and mutation type, etc..

### 4.1.2 Sample collection

Available plasma and re-biopsy tumor tissue samples (or cytological samples, pleural fluid etc., if tissue is not available) will be collected from patients who meet the eligibility criteria for testing period. Blood samples should be obtained following progression on a previous EGFR-TKI, but prior to dosing with AZD9291.

The sample requirements for each detection platform and for the plasma AZD9291 testing are as follows. Total 27ml blood will be collected at enrollment visit. (details please see the laboratory manual).

| | blood (ml) |
|---|---|
| Cobas | 5ml |
| Super-ARMS | 8ml |

| | |
|---|---|
| QuantStudio3D digital PCR | 4ml |
| NGS | 8ml |
| Plasma AZD9291 testing | 2ml |

FFPE tumor tissue samples (or cytological samples, pleural fluid etc.) will be collected at enrolment visit and at disease progression in sufficient amount (recommended 15 FFPE slices (needle biopsy) or 4 FFPE slices (surgical specimen), thickness 5um, tumor cells≥20%; or cytological samples like pleural fluid. Detail requirements please see the laboratory manual), and be tested by NGS to explore the mechanisms of acquired resistance in patients who received AZD9291 treatment.

Blood for dynamic monitoring of EGFR mutations (T790M, C797S etc.) will be collected at each treatment visit (every 6 weeks), at radiographic progression and 6w after radiographic progression (if patient continue treatment as judged by investigator). These samples will be tested by digital PCR and NGS retrospectively according to the testing plan (Table 2, details please see the laboratory manual).

Remain DNA samples (if any) will be retested by Bio-rad droplet digital PCR platform retrospectively for T790M and sensitizing mutations(if enough amount of samples) and data will be compared with testing results of other four platforms. For retrospective test on all the remain samples, patient who are still on AZD9291 treatment will be informed (or EC approve informed consent waiver); for patient who can't get in touch will apply informed consent waiver. But the investigator should review the medical record to see if the patient expressed any objection to use his/her remain samples for scientific research purpose. If such objection was recorded, then this patient’s remain samples should not be used.

All samples must be well labelled. A case report form (CRF) will be provided to fill in testing related data, and necessary information must be recorded in CRF and checked before transportation.

For the details about sample collection, label, record, package and transportation see the laboratory manual.

### 4.1.3 Mutation testing & Data management

Tumor DNA will be isolated from FFPE specimens and ctDNA will be recovered from plasma samples. DNA isolated from tissue will be qualified by measuring the A260/280 and A260/230. T790M and other mutations in plasma will be tested by different platforms: Cobas, Super-ARMS, digital PCR and NGS at enrolment visit. Remain DNA samples (if any) will be retested by Bio-rad droplet digital PCR platform retrospectively. Testing results and raw data will be transferred from central lab.

The following information should be recorded in the CRF and database: Subject's identity, EGFR mutation testing results (including quantitative results, if available), Sample information (including source of anatomical location and the date of collection), and etc.

### 4.2 Treatment period

Patient visits (e.g. physical exam, laboratory tests, etc.) must be performed according to the institutional standard of care and investigator's best medical judgment. AZD9291 re-supply must always be preceded by a treatment visit per Table 1.
Additionally, at each visit:

Drug accountability must be documented in the case report form (CRF) and necessary paper logs.

Patient needs to be screened for reportable safety events outlined in Section 6.

Tumour assessments (RECIST v1.1) described in Section 5 needs to be documented in the CRF.

Investigators are required to assess the patient's performance status and confirm that the patient continues to be deriving benefit from AZD9291 at the time of study drug re-supply.

If a patient withdraws from the treatment and/or completely from the study, the investigator will record the reason for withdrawal.

**Please note that if the reason for withdrawal is an event meeting the definition of SAE, it must be recorded in both the safety and clinical forms**

For patients lost to follow-up, every reasonable effort must be made to establish the survival status and document this in the CRF.

As an investigational drug, AZD9291 must be stored appropriately and dispensed from a secure storage area (or site pharmacy). Study sites are required to maintain accountability logs for drug receipt, dispensation, destruction and return (as applicable per local regulations).

AZD9291 may only be used for the specific patient enrolled into the study.

## 4.3 Follow-up period

Patients must be followed through the designated follow-up period (30 days post last dose of AZD9291) to collect SAEs occurring during this period and other required reporting per Section 6 and follow-up on any ongoing SAEs.

# 5. STUDY ASSESSMENTS

The Electronic Data Capture (EDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

The sources of information for all study variables collected for this study will be patient medical records or charts and patients surveys. All data collected will be entered by the investigator into a CRF. All patients receiving AZD9291 treatment will be followed from enrolment until completion of the study, discontinuation of AZD9291 administration (determined by investigator due to adverse events, toxicities or other relevant reasons), discontinuation due to disease progression, or death, whichever occurs earlier.

Study measures will be collected at baseline and during the follow-up period. For each patient, physicians will be required to provide date of enrolment, and thereafter during the follow-up visits, the date and outcome of the more recent disease assessment, and date of progression and death (if applicable). The variables described in the following sections will be collected to address the study objectives.

The study measures that will be assessed among patients participating in this study are listed below:

- **Baseline demographic characteristics**: patient characteristics including age, gender, race (if available or allowed by local regulations) will be collected
- **Smoking history**: non-smoker, ex-smoker and current smoker according to the status before AZD9291 treatment
- **T790M** and sensitizing mutations results and type of test performed
- **Relevant Medical history**: comorbidities and relevant medical history (this includes any chronic conditions currently requiring medication)
- **Disease characteristics**: tumor histology, stage at diagnosis, current stage, time of progression, WHO performance status at study enrollment and subsequent follow-up visits ("if patient will be followed)
- **Cancer treatment history**: first-line therapy type (targeted or non-targeted) and agents received, start and end-dates, subsequent-lines type and start and end-date, radiation therapy (yes/no), surgery (yes/no) received prior to study enrollment must be documented

For patients that are T790M mutation plasma test positive and receive AZD9291 treatment, the following will be measured during follow up:

- **Physical examination**: at baseline and at treatment discontinuation
- **Weight**: at each visit
- **Visual test:** at screening, a slit-lamp examination should be obtained. Ophthalmologic exams to be performed as clinically indicated. A 30-day follow-up assessment will be required if an on treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality
- **Relevant Concomitant medication:** in case of SAE and AEs.
- **AZD9291 dosing:** starting dose, dose adjustments, dose interruptions, dose discontinuation and reason for any dose change.
- **Tumor assessment (RECIST v1.1):** see section 5.1.
- **Progression follow-up**: after study medication discontinuation for reasons other than disease progression, the patient will continue tumor assessments and the physicians will report related data in the CRF at each follow-up visit.
- **Survival status**: patient survival status (dead, alive, unknown) at each follow-up must be documented in the CRF. The time from the date of first dose in the study until death will be used to evaluate OS. Lost to follow-up patients will be censored at last documented contact with patient status “alive”.
- **Laboratory assessments**: laboratory parameters will not be collected. If done, they will be assessed by the investigator as normal or abnormal and details about abnormality will be entered in the CRF

If Subject negative for T790M mutation in plasma by all four platforms is T790M positive in tissue and then receives AZD9291 monotherapy, the subject will have RECISTv1.1 assessment every 6 weeks (provided with free CT scan) and be followed for OS and data will be collected.

## 5.1 Efficacy assessments

The imaging modalities used for RECIST v1.1 assessments will be CT scan of the chest and abdomen (including liver and adrenal glands, ect.). The methods used at baseline for assessment of tumor burden (CT scan) must be used at each subsequent follow-up assessments. Any other sites where disease is suspected or known at baseline must also be imaged and additional sites of disease, confirmed at baseline not covered by the protocol specified anatomy, should be followed at the same scheduled visits as the other RECIST assessments.

For Investigator assessment, RECIST v1.1 criteria will be used to assess each patient's tumor response to treatment and allow calculation of PFS and ORR. The RECIST v1.1 guidelines for measurable, non-measurable, target and non-target lesions, and the objective tumor response criteria (complete response [CR], partial response [PR], stable disease [SD], or progression of disease [PD]) are presented in Appendix B.

## 5.2 Safety assessments

Not applicable.

## 5.3 Other assessments

Not applicable.

## 5.4 Pharmacokinetics

Not applicable.

## 5.5 Pharmacodynamics

Not applicable.

## 5.6 Pharmacogenetics

Not applicable.

## 5.7 Biomarker analysis

The subject's consent to the use of donated biological samples is mandatory.

According to the study plan, biological samples (tumour samples and plasma samples) will be collected and may be analysed for EGFR mutations (T790M, C797S etc.) and other exploratory biomarkers to assess correlations with disease activity, effects of study drug, and clinical outcomes.

### 5.7.1 Storage, re-use and destruction of biological samples

Samples will be stored until the end of the study, after which they will be returned to hospital sites as required or destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research that agreed by study steering committee.

### 5.7.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual.

### 5.7.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

### 5.7.4 Withdrawal of Informed Consent

If a subject withdraws consent, it must be clear if the subject agrees to store their samples or destroy the remaining specimen, and the action should be documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples at enrolment visit is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratories holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratories holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

# 6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

## 6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition

can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram).

## 6.2 Definitions of serious adverse event

An SAE is an event occurring from the time the patient signs informed consent (as per local regulations) through the end of the post-treatment follow-up visit (30 days post-last dose) or until disease progression, whichever is the latest, which fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix A to the study protocol.

### 6.2.1 Handling of deaths

All deaths that occur during the study or within the follow-up period after the administration of the last dose of AZD9291 (30 days post-last dose) or until disease progression, whichever is the latest, must be reported as follows:

- Death, which is unequivocally due to disease progression, must be reported to the study representative and must be documented in the CRF, but must not be reported as an SAE during the study.
- Where death is not clearly due to progression of the disease being treated as part of the study, the primary and most likely event causing the death must be reported to AstraZeneca's representative as an SAE within 24 hours. The report must contain a comment regarding the co-involvement of progression of disease, if appropriate, and must assign a single primary cause of death together with any contributory causes.
- Deaths with an unknown cause must always be reported as an SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results must be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

### 6.2.2 Hy's Law

Cases where a subject shows an AST or ALT ≥3xULN or total bilirubin ≥2xULN may need to be reported as SAEs. The investigator is responsible for, without delay, determining whether a subject meets potential Hy's law (PHL) criteria. Details of identification of PHL cases and actions to take are detailed in Appendix D. Those SAE will be collected until 30 days post last dose of study medication.

## 6.3 SAEs related to study procedures or conduct of a study

An SAE related to a study procedure is considered as a SAE that has arisen as a direct consequence of the subject participating in the study, for any reason other than due to receipt of an Investigational Medicinal Products (IMP).

## 6.4 Recording of adverse events

### 6.4.1 Time period for collection of adverse events

Adverse Events, including Serious Adverse Events, will be collected from time of signature of informed consent, throughout the treatment period and up to and including the 30-day follow up period*. All ongoing and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution. After any interim analysis, any ongoing AEs/SAEs need to be unlocked and followed for resolution.

*Exception: all AEs/SAEs has reported in ASTRIS main study should not be reported in current study.

### 6.4.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the time of the 30 day follow-up, must be followed up by the investigator through to resolution, and whilst the database is open should be recorded on the database.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

### 6.4.3 Adverse events after the 30 day follow-up period

At any time after a patient has completed the study, if an investigator learns of any SAE including death, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca, Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut-off and/or post study completion then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.

Otherwise after study treatment completion (i.e. after any scheduled post treatment follow-up period has ended), there is no obligation to actively report information on new AEs or SAEs

occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow-up period (30 days).

### 6.4.4 Causality collection

The investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

## 6.5 Reporting of serious adverse events

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

**Contact information of AZ PV China Team:**

Fax: +86 21 38683551;

E-mail: **China.AZDrugSafety@astrazeneca.com**;

Tel: +86 21 52929866 · +86 21 58385073（Emergency）

## 6.6 Management of toxicities related to AZD9291

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade), where the investigator considers the event of concern to be specifically associated with AZD9291 (and not attributable to the disease or disease-related processes for which patient is being treated), dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

If the toxicity resolves or reverts to CTCAE grade ≤ 2 within 3 weeks of onset, treatment with AZD9291 may be restarted at the same dose (80 mg, daily) or a lower dose (40 mg, daily) using the rules below for dose modifications(Table 1) as per the investigator's evaluation and/or in discussion and agreement with the study Medical Monitor as needed. There will be

no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption. Once a dose reduction is implemented, the dose of AZD9291 cannot be reverted back to 80 mg.

If the toxicity does not resolve to CTCAE grade ≤ 2 after 3 weeks, then the patient must be withdrawn from the study treatment and kept in observation until resolution of the toxicity.

**Table 3 Dose Interventions**

| Intervention | AZD9291 Dose |
|---|---|
| Starting Dose | 80 mg daily |
| Reduced Dose | 40 mg daily |

If an event subsequently requires dose interruption, AZD9291 may restart at the same dose or the reduced dose, on resolution/improvement of the event at the discretion of the investigator.

### 6.6.1 Pulmonary Symptoms

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease are observed, the administration of AZD9291 needs to be interrupted and the study Medical Monitor must be informed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. The results of the full diagnostic workup (including high-resolution computed tomography, blood and sputum culture, haematological parameters) will be recorded in the CRF by the investigator. Where ILD is suspected, local practice must be followed in discussion with the study Medical Monitor. In the absence of a confirmed diagnosis of ILD, AZD9291 may be restarted following consultation with the study Medical Monitor. In case of a confirmed diagnosis of ILD, AZD9291 must be permanently discontinued. (refer to "Guidance for the Management of AE in studies using 80mg AZD9291")

### 6.6.2 QTc Prolongation (using Fredericia's formula –QTcF–)

Patients with Grade 3 QTcF with QTcF prolongation (i.e., confirmed QTcF prolongation to > 500 ms absolute or a > 60 ms increase from baseline) should have AZD9291 interrupted and regular ECGs performed until resolution to baseline. If the QTcF interval resolves to Grade 1 (<481 msec), AZD9291 may be restarted at the reduced dose of 40 mg. If the QT prolongation does not resolve to ≤CTCAE grade 1 (<481 msec) after 3 weeks, then the patient will be permanently withdrawn from AZD9291 and observed until resolution of the toxicity.

All QTcF prolongation of >470 ms at any point during the study must be reported to AstraZeneca, and ECGs sent to the Study Team for further analysis. This does not alter the management guidance outlined above.

### 6.6.3 Corneal Ulceration

Following an ocular event, the results of eye investigation must be recorded in the CRF by the investigator. Patients experiencing corneal ulceration will not be permitted to restart AZD9291 treatment.

### 6.6.4 Skin reactions

Recommendations for appropriate management of skin reactions, including guidance on dose-adjustments for clinically significant and/or intolerable skin reactions that are considered by the investigator to be causally related to AZD9291 will be provided to clinicians.

### 6.6.5 Diarrhoea

Recommendations for appropriate management of diarrhoea, including uncomplicated CTCAE grade ≤2, and dose-adjustments for AEs of diarrhoea that are of CTCAE grade ≥3 or that are clinically significant and/or intolerable and considered by the investigator to be causally related to AZD9291, will be provided to participants in the study.

For further guidance on skin reactions and diarrhoea, please refer to "Guidance for the Management of Adverse Events in Studies using 80 mg AZD9291"

## 6.7 Study governance and oversight

### 6.7.1 Steering Committee

A Steering Committee comprising of the Principal Investigators for this study will provide advice on any aspect of the study design or conduct based on requests from the sponsor and assure consistency across the entire AZD9291 pivotal programme.

### 6.7.2 Data Monitoring Committee

This is an open-label (non-randomised) testing and treatment study in 250 patients from the ASTRIS China study screening. Data Monitoring Committee will not be used in this study.

# 7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

## 7.1 Identity and dose of investigational product– AZD9291

AZD9291 will be supplied as tablets for oral administration as a single daily dose of 80 mg. Each bottle will contain sufficient AZD9291 treatment for 21 days, plus overage. 40 mg tablets will be supplied as needed upon request to the AstraZeneca representative.

| Investigational product | Dosage form and strength |
|---|---|
| AZD9291 | 40 mg Tablets |
| | 80 mg Tablets |

The tablets can be taken with or without food and should be swallowed whole with water. The tablet should not be crushed, split or chewed.

If the patient is unable to swallow the tablet, it may first be dispersed in 50 mL of non-carbonated water. The tablet should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional half a glass of water should be added to ensure that no residue remains and then immediately swallowed.

If administration via nasogastric tube is required, the same process as above should be followed but using volumes of 15 mL for the initial dispersion and 10 mL for the residue rinses. The total liquid should be administered as per the nasogastric tube instructions with appropriate water flushes.

The initial dose of AZD9291 80 mg daily can be reduced to 40 mg once daily under circumstances described in Section6.7.

Doses should be taken approximately 24 hours apart at the same time point each day. Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the scheduled dose time, the missed dose must not be taken, and patients must be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their AZD9291 treatment, they must not make up for this dose, but must take the next scheduled dose.

Any change from dosing schedule, dose interruptions, or dose reductions must be recorded in the CRF.

Tablets will be packed in high-density polyethylene bottles with child-resistant closures. Bottles will be dispensed to patients in the packaging provided. The packaging includes bottles, caps and a label. Bottle tampers must not be broken prior to dispensing AZD9291 to a patient.

Additional information about AZD9291 may be found in the IB.

## 7.2 Labelling

Labels for AZD9291 will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The label will include the following information the Name of the Sponsor, Protocol Code, For Clinical Trial use only, and/or any other market specific requirements.

Patient’s leaflet will be inserted if required per local regulations

## 7.3 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottles specifies the appropriate storage.

## 7.4 Compliance

The administration of AZD9291 must be documented in the appropriate sections of the CRF. Patients must return all unused IP and empty containers to the investigator.

## 7.5 Accountability

The study drug provided for this study will be used only as directed in the study protocol.The study personnel will account for all study drugs dispensed to and returned from the subject.

The study personnel at the investigational site will account for all treatments dispensed and for appropriate return or destruction. The site is required to maintain documentation of the delivery, return and destruction of IP. AstraZeneca representatives will review and collect this documentation.

## 7.6 Concomitant and other treatments

Concomitant treatments, other than anti-cancer treatments, should be taken according to local medical practice. There are no restrictions on concomitant use in this study except per exclusion criteria. However, it is advised that those medical products and other products known to have interactions with AZD9291 should be avoided (see Appendix C).

# 8. STATISTICAL ANALYSES BY ASTRAZENECA

## 8.1 Statistical considerations

Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized before database lock.

In general, descriptive statistics will be provided for the data collected. For continuous variables, mean, standard deviation, median, quartiles, minimum and maximum will be provided, and for categorical variables, frequency counts and percentages for each category will be provided. Data will be examined for skewness, outliers, and systematic missing data. Transformations will be undertaken as needed.

## 8.2 Sample size estimate

Approximately 250 eligible patients from 9 hospitals will be enrolled to this study. Assuming the concordance of each platform of Super-ARMS, digital PCR, and NGS with Cobas ranges

from 70% to 90%, the precision of estimation (i.e., half-length of 95% confidence interval <CI>) will be around 3.7% to 5.7%.

| Platforms | Possible concordance with Cobas | Precision of estimation (i.e., half length of 95% CI) |
|---|---|---|
| Super-ARMS | 70% | 5.7% |
| Digital PCR | 80% | 5% |
| NGS | 90% | 3.7% |

Assuming that around 40% to 60% (i.e., 100 ~ 150) patients will have T790M resistance mutation and receive AZD9291, the median PFS is around 9 to 11 months, and that disease progression or death will be observed for 60% of the patients after 12-month follow up of the last enrolled patients for the primary analysis of PFS data, the 95% CI of estimation of median PFS is illustrated in the table below:

| | | 95% CI of median PFS* | | |
|---|---|---|---|---|
| No. patients | No. events | Median PFS: 9 months | Median PFS: 10 months | Median PFS: 11 months |
| 100 | 60 | 7.0 – 11.6 | 7.8 – 12.9 | 8.5 – 14.2 |
| 125 | 75 | 7.2 – 11.3 | 8.0 – 12.5 | 8.8 – 13.8 |
| 150 | 90 | 7.3 – 11.1 | 8.1 – 12.3 | 8.9 – 13.5 |

*Based on the formula in Collett 1994 (D. Collett et al., 1994).

## 8.3 Definitions of analysis sets

The full analysis set (FAS) will contain all patients who are eligible for the study and have any valid data of T790M mutation status. The FAS will be used for the analysis of biomarker data and others collected at screening visit.

The As-treated analysis set will contain all patients who take at least one dose of AZD9291. It will be used for the analysis of data collected during treatment and follow up period.

## 8.4 Outcome measures for analyses

Analysis will be conducted to evaluate the following as available in the CRF and database:

- Baseline characteristics: demographics, relevant medical history, disease characteristics, cancer treatment history, smoking history.

- T790M and sensitizing mutations plasma testing results by Cobas, Super-ARMS, digital PCR, and NGS
- T790M and sensitizing mutations tissue (or cytological samples, pleural fluid etc.) testing results (if available)
- Exposure to AZD9291
- Overall Survival (OS):
  Overall survival is defined as the time from the date of first dose of AZD9291 in this study until death due to any cause. Any subject not known to have died at the time of analysis will be censored at the last recorded date on which the subject was known to be alive.
- Progression Free Survival (PFS):
  PFS is defined as the time from first dose of AZD9291 in this study until the date of disease progression as recorded in CRF or death (by any cause in the absence of progression) regardless of whether the subject withdraws from therapy or receives another anti-cancer therapy prior to progression. Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment. (or, if no tumor assessments are performed after the baseline visit, at the date of baseline visit).
- Objective Response Rate：Objective Response Rate is defined as the number (%) of patients with measurable disease with at least 1 visit response of CR or PR. Data obtained until progression or last evaluable assessment in the absence of progression will be included in the assessment of ORR. However, any CR or PR which occurred after a further anti-cancer therapy will not be included in the numerator for the ORR calculation (where the As-treated analysis set will be the denominator).
- Percentages of EGFR mutations (C797S and T790M etc., respectively) at different time point by NGS and digital PCR, respectively, during dynamic monitoring.
- Distribution of NGS testing results (contain 295 genes) at baseline and at PD.

## 8.5 Methods for statistical analyses

All data will be presented for the full analysis set. The concordance of T790M resistance mutation testing between the Cobas test and each of other platforms will be calculated. The Kappa coefficient will also be calculated to measure the agreement. The sensitivity, specificity, positive predictive value, and negative predictive value of each testing platform (Super-ARMS, digital PCR, and NGS) will be calculated with the Cobas test as the reference.

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, interquartile

range (Q1, Q3), minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. The 95% confidence interval (CI) will be calculated as appropriate. PFS and OS, respectively, will be summarized using Kaplan-Meier estimates of the median time to event (progression and death) and quartiles together with their 95% confidence intervals. The chi-square test will be used to compare the sensitivity, specificity, and concordance between any of the two platforms using Cobas as reference testing.

### 8.5.1 Analysis of the primary variable (s)

The concordance of T790M resistance mutation testing between the Cobas test and each of other platforms (Spuer-ARMS/digital PCR/NGS). It will be calculated according to the following formula:

> Concordance (%)=(number of patients with same T790M mutation status based on Cobas and each other platform)/(total number of patients in the FAS with evaluable testing results) ×100%.

PFS will be summarized using Kaplan-Meier (KM) estimates of the median time to progression or death and quartiles together with their 95% confidence intervals. KM estimates of PFS rate at appropriate time points (to be defined in SAP) will be presented as well. Plot of the KM PFS curve will be produced.

### 8.5.2 Analysis of the secondary variable(s)

The sensitivity, specificity, positive predictive value, negative predictive value of Super-ARMS/digital PCR/NGS will be calculated according to the following formulae by using Cobas as the reference:

> Sensitivity (%)=(number of patients with T790M mutation positive based on Cobas and each other platform)/(number of patients with T790M mutation positive based on Cobas) ×100%
>
> Specificity (%)=(number of patients with T790M mutation negative based on Cobas and each other platform)/(number of patients with T790M mutation negative based on Cobas) ×100%
>
> Positive predictive value (%)=(number of patients with T790M mutation positive based on Cobas and each other platform)/(number of patients with T790M mutation positive based on each other platform) ×100%
>
> Negative predictive value (%)=(number of patients with T790M mutation negative based on Cobas and each other platform)/(number of patients with T790M mutation negative based on each other platform) ×100%

The chi-square test will be used to compare the concordance, sensitivity, and specificity between any of the two platforms using Cobas as reference testing in an exploratory manner.

OS will be summarized using Kaplan-Meier estimates of the median time to death and quartiles together with their 95% confidence intervals. KM estimates of OS rate at appropriate time points (to be defined in SAP) will be presented as well. Plot of the KM overall survival curve will be produced.

ORR will be summarized with frequency counts and percentages for each category. The 95% CI will be provided as appropriate.

### 8.5.3 Exploratory analysis

The proportion of patients with each EGFR mutation (C797S and T790M etc.) as well as other genetic and proteomic markers at different time point will be calculated as each EGFR mutation or marker divided by total number of patients with evaluable testing results. The data will be presented for the overall population (i.e., As-treated analysis set) as well as by subgroups such as short-term and long-term survivors.

- **Long-term survivors group (case):** EGFR M+ aNSCLC patients who continuously received AZD9291 for at least 18 months without evidence of PD

- **Rapid PD group (control):** EGFR M+ aNSCLC patients who had undergone PD after AZD9291 treatment≤3 months

  Testing data of cytological samples (if collected) may be analyzed either separately or together with tissue samples. Data of clinical outcomes (ORR, PFS and OS) will be described separately for subjects that are negative for T790M mutation in plasma by all four platforms but positive in tissue and then receive AZD9291 monotherapy. The concordance, sensitivity, specificity, PPV, NPV of EGFR mutation plasma testing by Bio-rad droplet digital PCR using other plasma tests or tissue test as reference will be calculated according to the similar formulas as above. The efficacy of patients who receive AZD9291 monotherapy and are T790M positive patient by each of the five platforms, respectively, will be analyzed same as above. Details will be specified in SAP.

### 8.5.4 Analysis timing

Four analyses are planned:

- The primary analysis of T790M testing concordance of four platforms and other testing data at enrollment visit will be conducted after the last patient is enrolled.

- The primary analysis of PFS data will be conducted after 12-month follow up of the last enrolled patients, assuming that 60% of the patients who receive AZD9291 will have disease progression or death at this time.

- The exploratory analysis of T790M testing concordance and other testing data at enrollment visit by Bio-rad droplet digital PCR will be conducted once the data is available.

- The final analysis will be conducted in about Q3 2019 when the last patient is followed up for 18 months.

# 9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

## 9.1 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the EDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

## 9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)

- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and

disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

### 9.2.1 Source data

Study sites will maintain source data in accordance with Good Clinical Practice (GCP) or local regulations.

### 9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

### 9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

## 9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in Quarter 4 2016 and to end by Quarter 4 2019.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD9291.

## 9.4 Data management by AstraZeneca or delegate

Data management will be performed by AstraZeneca Data Management Centre staff or other party, according to the Data Management Plan.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

**Data associated with human biological samples**

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca.

# 10. ETHICAL AND REGULATORY REQUIREMENTS

## 10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

## 10.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca or its representative will not provide patient information to patients, any insurance company, any employer, their family members, general physician or to any other third party, unless required to do so by law**.**

Precautions are taken to preserve confidentiality and prevent data being linked to the identity of the patient. Also Regulatory authorities may require access to the relevant files.

## 10.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff , who are authorised by principal investigator.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the site Ethical Committee or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

## 10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

## 10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca or its representative will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

## 10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

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