AstraZeneca

Statistical Analysis Plan

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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

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Updated by Tigermed Study Statistician

Joe Yao	Date

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Approved by AstraZeneca Study Statistician

Yi Chen	Date

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AstraZeneca Product Statistician

Rosemary Taylor	Date

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List Of Abbreviations

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
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

Abbreviation or special term	Explanation
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
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
WHO DDE	WHO Drug Dictionary Enhanced

AMENDMENT HISTORY

Version	Brief description of change
1.0	NA
2.0	Added the analysis for exploration (Post-hoc/Ad-hoc analysis), removed safety analysis

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary Objectives:	Outcome Measure:
To evaluate concordance of An amino acid substitution at position 790 in EGFR, from a Threonine to a Methionine (T790M) plasma mutation testing between the Cobas test and each of the other platforms: Super-ARMS, digital PCR and NGS.	Concordance
To assess the efficacy of AZD9291 monotherapy by assessment of PFS in adult patients with advanced or metastatic Non-small Cell Lung Cancer (NSCLC), who have received prior Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (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 Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)

1.1.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To evaluate the sensitivity, specificity, positive predictive value (PPV) and 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 Objective Response Rate (ORR) and Overall Survival (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

1.1.3 Safety objectives

N/A

1.1.4 Exploratory objectives

Exploratory objectives:	Outcome Measure:
To dynamically monitor EGFR mutations by NGS and digital PCR in Circulating Tumor DNA (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 Progression of Disease (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

1.2 Study design

This is an open-label, multi-center, testing and treatment study in 250 locally advanced or metastatic NSCLC patients with a documented EGFR sensitive mutation and progression on a 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 the other three platforms as one of the primary endpoints. Sensitivity, specificity, NPV, and PPV of the testing methods are defined as secondary endpoints.

Patients who are T790M mutation positive via a plasma test by any one of the four platforms and meet the eligibility criteria for the treatment period will receive AZD9291 treatment in the 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 CSP section 3.11). OS and ORR are defined as secondary endpoints.

1.3 Number of subjects

Approximately 250 eligible patients from 9 hospitals are planned to be enrolled into 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 a 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-months of follow up of the last enrolled patient 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).

2. ANALYSIS SETS

2.1 Definition of analysis sets

The full analysis set (FAS) will contain all patients who are eligible for the study and have any valid plasma data of T790M mutation status. The FAS will be used for the analysis of biomarker data and other data collected at the 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 the treatment and follow up period.

As the purpose of analysis, subjects in as-treated analysis set should be positive for T790M mutation in plasma by at least one of the four platforms. Subjects who are negative for T790M mutation in plasma by all four platforms but positive in tissue and then take at least one dose of AZD9291 (Tissue-Positive-Only) will be described separately.

2.2 Violations and deviations

Protocol deviations will be identified by the Medical Monitor team of this project and finalized at the Data Review Meeting before the database lock.

The important protocol deviations will be tabulated and listed.

3. PRIMARY AND SECONDARY/EXPLORATORY VARIABLES

Primary variables:

- Concordance estimated by T790M plasma testing results between Cobas and each of the other three platforms: Super-ARMS, digital PCR, and NGS.

- Progression Free Survival (PFS): PFS is defined as the time from first dose of AZD9291 in this study until the date of investigator assessed disease progression according to RECIST 1.1 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 first dose date). If death/progression was observed after two or more missing visits (cycle, 6 weeks + 1 weeks), subject was censored at the last assessment visit before these missing visits.

Secondary variables:

- Testing sensitivity, specificity, PPV, and NPV estimated by T790M plasma testing results by Cobas, Super-ARMS, digital PCR, and NGS.

- 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 as assessed by investigator according to RECIST 1.1. 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).

- 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.

Exploratory variables:

- Concordance estimated by T790M plasma testing results between Cobas and ddPCR.

- Testing sensitivity, specificity, PPV, and NPV estimated by T790M plasma testing results by Cobas and ddPCR.

- Percentages of EGFR mutations (C797S and T790M etc., respectively) at different time points by NGS and digital PCR, respectively, during dynamic monitoring.

- Distribution of NGS testing results (contain 295 genes) at baseline and at progressive disease.

- Key genetic and proteomic markers including, but not limited to, EGFR mutations, which were different between long-term survivors and rapid PD patients.

4. ANALYSIS METHODS

4.1 General principles

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 the 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. Data will be examined for skewness, outliers, and systematic missing data as needed. Transformations will be undertaken as needed.

Unless otherwise specified, two-sided 95% confidence intervals via exact (Clopper-Pearson for percentages) method will be calculated as appropriate.

The baseline will be the last non-missing assessment before the first dosing date unless otherwise specified.

Time windows will be defined for any presentations that summarise values by visit (such as WHO performance status, weight, Ophthalmologic assessment, plasma NGS and digital PCR). The following conventions should also apply:

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the time window should be based on the actual date and not the intended date of the visit.

- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 1). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day.

- If there is more than one value per patient within a time window then the closest value should be summarized, or the earlier in the event the values are equidistant from the nominal visit date.

For example, the visit windows for WHO performance status during treatment phase are:

- Week 6 (Day 42), visit window: Day 1 – Day 63

- Week 12 (Day 84), visit window: Day 64 – Day 105

- Week 18 (Day 126), visit window: Day 106 – Day 147

- Etc.

In general, no data imputation will be done. The number of subjects with missing data will be reported in the statistical description.

Analyses will be performed by using SAS 9.4.

4.2 Analysis methods

4.2.1 Analysis Timing

Two analyses are planned:

- The primary analysis (analysis 1) of T790M testing concordance and other testing data at the enrollment visit will be conducted after the last patient is enrolled and all test results at the enrolment visit are obtained.

- The final analysis (analysis 2) will be conducted in about Q4 2021 after the database is locked.

4.2.2 Analysis of the primary variable (s)

4.2.2.1 Concordance

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

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

According to the analysis purpose defined in section 4.2.1, analysis will be performed on the FAS in analysis 1 and only subjects with testing results of both Cobas test and other platform (Super-ARMS or digital PCR or NGS) will be included.

The exact (Clopper-Pearson) confidence limits for this binomial proportion will be calculated.

As a supportive analysis, the Kappa coefficient and related 95% confidence interval will also be calculated to measure the agreement.

4.2.2.2 PFS

According to the analysis purpose defined in section 4.2.1, PFS analysis will be performed on the As-treated analysis set in analysis 2. 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 (3 months, 6 months, 9 months, and 12 months and every 6 months afterwards if applicable) will be presented as well. Plots of the KM PFS curve will be produced.

The definition of censoring for PFS was in section 3 and PFS will be calculated as (the earlier of disease progression date or death date or censored date - the first dose date) + 1.

4.2.3 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%

According to the analysis purpose defined in section 4.2.1, analysis will be performed on FAS in analysis 1 and only subjects with testing results of both Cobas test and other platform (Spuer-ARMS or digital PCR or NGS) will be included.

OS and ORR analysis will be performed on the As-treated analysis set in analysis 2. 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 (6 months, 12 months, 18 months, and 24 months and every 6 months afterwards if applicable) will be presented as well. Plot of the KM overall survival curve will be produced.

The definition of censoring for OS was in section 3 and OS will be calculated as (the death date or censored date - the first dose date) + 1.

ORR, as well as the best response of CR, PR, SD, PD, and NE respectively, will be summarized with frequency counts and percentages for each category. The exact (Clopper-Pearson) confidence limits will be provided as appropriate.

The same analysis for OS and ORR will also be performed on the Tissue-Positive-Only subset.

4.2.4 Exploratory analysis

The concordance of T790M resistance mutation testing between the Cobas test and ddPCR will be calculated and analyzed as section 4.2.2.1.

The sensitivity, specificity, positive predictive value, negative predictive value of Super-ARMS/digital PCR/NGS against ddPCR will be calculated according to the following formulae by using Cobas as the reference. The formulas and analysis methods will be referred to section 4.2.3.

The details methods how to analysis other exploratory variables [Percentages of EGFR mutations (C797S and T790M etc., respectively) at different time points by NGS and digital PCR, respectively, during dynamic monitoring, Distribution of NGS testing results at baseline and at progressive disease, and Key genetic and proteomic markers including, but not limited to, EGFR mutations, which were different between long-term survivors and rapid PD patients] will be plan in a separated file.

4.2.5 Subject disposition

The frequency counts and percentages of subjects enrolled, included in FAS, included in As-treated analysis set, undergone each platform test, treated with AZD9291, switching to other anti-cancer therapy, undergone disease progression, withdrew, and dead will be calculated and presented in analysis 1 and analysis 2.

Data list on patients with screening failure will be presented.

4.2.6 Demographics and baseline characteristics

Demographics information, such as age, gender, race, weight, and WHO performance status will be described according to the general principles in section 4.1. 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 the frequency counts and percentages for each category. According to the analysis purpose defined in section 4.2.1, this analysis will be performed on FAS (analysis 1) and As-treated analysis set (analysis 2), respectively.

4.2.7 Other baseline information collected

Other information collected at baseline, such as substance use (Nicotine), previous therapy and surgery, relevant medical history (past and current), will be described according the general principles in section 4.1. 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 the frequency counts and percentages for each category. According to the analysis purpose defined in section 4.2.1, this analysis will be performed on FAS (analysis 1) and As-treated analysis set (analysis 2), respectively.

Previous therapy will be coded by the latest version of WHO Drug Dictionary Enhanced (WHO DDE) and the frequency counts and percentages of subjects with each preferred term

(PT) within each Anatomical-Therapeutic-Chemical classification system (ATC02) will be summarized. Relevant medical history and previous surgery (if applicable) will be coded by MedDRA (the latest version) and the frequency counts and percentages of subjects with each preferred term (PT) within each system organ class (SOC) will be summarized.

4.2.8 Treatment exposure

Duration of exposure, including total exposure and actual exposure, as well as treatment compliance will be described according the general principles in section 4.1, i.e., the number of observations, mean, standard deviation, median, interquartile range (Q1, Q3), minimum, and maximum will be presented. The frequency counts and percentages of subjects with each dose adjustment reason within dose adjustment type will be summarized.

Total Exposure to AZD9291 will be defined as time (days) from the first dose to the last dose:

- Total exposure = last dosing date where dose > 0 mg – first dosing date where dose > 0 mg + 1

Actual exposure to AZD9291 will be time (days) from first dose to last dose, taking into account the number of days where no dose was taken.

- Actual exposure = last dosing date where dose > 0 mg – first dosing date where dose > 0 mg + 1 – total duration of dose interruption (i.e. number of days with dose = 0 mg)

Treatment compliance (%) is defined as the number of administered doses of AZD9291 (80 mg or 40 mg) taken as a proportion of the scheduled expected number of doses.

Overdose information will be reported as data listing, refer to section 4.2.15.

According to the analysis purpose defined in section 4.2.1, this analysis will be performed on the As-treated analysis set (analysis 2)

4.2.9 Post-hoc and ad-hoc analysis

This section describes additional analysis which was not planned in the protocol.

On subjects in the Tissue-Positive-Only subset, the same analysis for PFS (refer to section 4.2.2.2) will also be performed.

For T790M plasma positive subjects with different sensitivity mutations testing results (19del positive, L858R positive, or other positive) at baseline, the PFS will be analyzed according to section 4.2.2.2.

The ORR (according to section 4.2.3) will be analyzed for subjects with different baseline characteristics (T790M resistance mutation test results by 4 platforms, different Digital PCR measurement results, different NGS measurement results, T790M and EGFR amplification status, mutation other than T790M, T790M tissue status, previous chemotherapy, and previous radiotherapy).

PFS and ORR of subjects with positive mutations testing (L858R, 19del, G719X, L861Q, exon 20 insertion etc. at least one other than T790M) results at baseline will be analyzed according to the mutations testing results at different time points, including but not limited to progression, visit before progression, week 6, and best response. The PFS will be analyzed according to section 4.2.2.2. Time to appearance of resistance related gene alterations, for instance C797S etc., will be analyzed.

For platforms NGS and digital PCR, three different cut off values (0.1%, 0.3% and 0.5%), the PFS (HR) and ORR in subjects with values above and below the cut off will be displayed by plots. The cut off at 0.1% will be considered primary and the other cut offs will only be explored if 15% subjects change their classification (from below to above the cut off or vice versa) when the new cut off is considered.

For the subgroup analyses on time-to-event data, if there are too few events available (less than 20 events across both treatment groups in a level of a subgroup), the survival analyses (e.g. KM estimations, HR and CI) will not be produced for that subgroups. In this case, only descriptive summaries (e.g. events number and events rate) will be provided.

If the sub-group contains the majority of the overall population (for example, if the subgroup contains 95% of the FAS), the sub-group analysis will not be performed.

The EGFR T790M mutation status of subjects with chemotherapy or EGFR-TKI as the latest therapy, different histology types, and different metastasis status before T790M mutation test will be presented separately.

The duration from previous disease progression to T790M mutation test will be described by EGFR T790M mutation status (positive or negative).

4.2.10 Data listing

All data to be analyzed in the sections above will be presented as data listings as well as other related information.

5. INTERIM ANALYSES

No interim analyses are planned.

6. CHANGES OF ANALYSIS FROM PROTOCOL

Only two analyses would be done according to the decision of study team. The first analysis was executed per protocol. The second analysis planned in protocol was cancelled due to HGR resubmission. The third analysis planned in protocol is the second formal analysis executed actually, which will be conducted after the database is locked.

According to the exploration purpose of study team, some post-hoc and ad-hoc analysis will also be executed and they were listed in section 4.2.9 (Post-hoc and ad-hoc analysis) besides the other ones planned in protocol.

7. REFERENCES

This SAP is according to CSP version 3.0 (25Aug2017).

D. Collett et al., 1994
D. Collett, Chapman & Hall. Modelling Survival Data in Medical Research. London, 1994.

8. APPENDIX

8.1 Analysis Dataset Specification

Refer to file d5160c00042-analysis-datasets-specification.xlsx.

8.2 Table, Figure, and Listing mock-up

Refer to file d5160c00042-table-figure-listing-toc.xlsx

Refer to file d5160c00042-table-figure-listing-mock-up.docx

8.3 Statistical analysis plan for NGS

Refer to file d5160c00042-statistical-analysis-plan_NGS.docx