- **Protocol number:** D5160C00022
- **Document title:** Open Label, Multinational, Multicenter, Real World Treatment Study of Single Agent AZD9291 for Patients with Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Prior Therapy with an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI).
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Real World Treatment Study – Statistical Analysis Plan (for the final analysis)

Drug Substance	AZD9291
Study Code	D5160C00022
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Open Label, Multinational, Multicenter, Real World Treatment Study of Single Agent AZD9291 for Patients with Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Prior Therapy with an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
AESI	Adverse Event of Special Interest
BCR	Best Clinical Response
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CT	Computer Tomography
CTCAE	National Cancer Institute Common Terminology Criteria for AEs
ECG	Electocardiogram
EGFR	Epidermal Growth Factor Receptor
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose -Positron Emission Tomography
ICH-GCP	International Conference on Harmonisation - Good Clinical Practice
ILD	Interstitial Lung Disease
IVRS/IWRS	Interactive Voice Response System/ Interactive Web Response System
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PT	Preferred Term
PMDA	Pharmaceuticals and Medical Devices Agency
PFS	Progression Free Survival
QTc	The QT interval corrected for heart rate

Abbreviation or special term	Explanation
QTcF	QT interval corrected per Fredericia's formula
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	A commercially available integrated system of software products, commonly used for reporting and analysis of Clinical Studies
SOC	System Organ Class
TKI	Tyrosine Kinase Inhibitor
TTD	Time to Treatment Discontinuation
WHO	World Health Organization

1 STUDY DETAILS

1.1 Study Objectives

The primary objective of this study is to assess the efficacy and safety of single agent AZD9291 in a real world setting in adult patients with advanced or metastatic, epidermal growth factor receptor (EGFR) T790M mutation-positive Non-Small Cell Lung Cancer (NSCLC), who have received prior EGFR-tyrosine kinase inhibitor (TKI) therapy.

1.2 Study Design

This is an open-label, single-arm, multinational, multicenter, real world treatment study. The target patient population is adult patients (fulfilling the definition of "age of majority" per local regulations) with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC with a confirmed T790M mutation, who have received prior EGFR-TKI therapy.

1.3 Number of Patients

Overall Survival (OS) is the primary efficacy endpoint for this study. Median OS is assumed to be approximately 21-25 months in patients with advanced or metastatic EGFR T790M mutation-positive NSCLC who have received prior therapy with an EGFR-TKI and are receiving treatment with AZD9291. While the sample size is not known a priori illustrations of the precision with which OS could be calculated from this real world study are given in the table below. These illustrations assume a study length of 58 months with non-uniform accrual over 40 months and that OS is exponentially distributed.

N	21 Months OS		23 Months OS		25 Months OS	
	n events	95% CI median OS*	n events	95% CI median OS*	n events	95% CI median OS*
500	313	18.8-23.5	297	20.5-25.8	283	22.3-28.1
1000	627	19.4-22.7	595	21.2-24.9	566	23.0-27.1
1500	941	19.7-22.4	893	21.5-24.6	800	23.3-26.8
2000	1255	19.9-22.2	1191	21.7-24.3	1133	23.6-26.5
3000	1883	20.1-22.0	1787	22.0-24.1	1700	23.8-26.2
3500	2197	20.1-21.9	2085	22.0-24.0	1983	23.9-26.1

*95% CI is based on the formula in Collet 1994 (Collett, 1994)

Therefore if 3500 patients enter the study globally and the median OS is 25 months the 95% confidence interval (CI) around this survival figure would be approximately 23.9-26.1 months, assuming 1983 OS events (57% maturity). For Europe, assuming recruitment of 1000 patients and 566 OS events, the equivalent 95% CI would be approximately 23.0-27.1 months.

2 ANALYSIS SETS

As this is a real world study investigating the efficacy and safety of AZD9291, all analyses will be performed on the full analysis set, unless otherwise indicated.

2.1 Definition of analysis set

Full Analysis Set (FAS)
The full analysis set will include all patients who received at least one dose of study treatment (i.e. with at least one start date in the Administration of the Study drug page in the CRF).

2.2 Violations and deviations

All major deviations related to the study inclusion or exclusion criteria and study conduct will be listed and summarised.

The following general categories will be considered major deviations. This list is not exhaustive and additional important deviations may be added prior to database lock.

- Informed consent procedure deviation Missing subject' signature from the informed consent document or other International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) violation related to informed consent; laboratory or urinalysis samples or electocardiogram (ECG) date before informed consent date and not performed per standard of care but on study purpose)
- Eligibility criteria deviation (any inclusion criteria not met or exclusion criteria met)
- Prohibited medication deviation (e.g., patients received other anticancer agents, investigational agents, or radiotherapy while on study treatment)
- Procedures/Tests deviation (ECG or ophtalmologic assessment or WHO performance status not performed at screening visit)
- Investigational product administration deviation (Overdose; Screening assessment date not within 28 days before start of treatment; Incorrect procedure for T790M obtainment; New or worsening pulmonary symptoms or radiological abnormality suggestive of Interstitial Lung Disease (ILD) observed, but study treatment not interrupted; Patient experiencing grade 3 QT interval corrected per Fredericia's formula (QTcF) with QTcF prolongation, but study treatment not interrupted)
- Withdrawal criteria deviation (Any withdrawal criteria met)
- Adverse Event (AE) / Serious Adverse Event (SAE) deviation (SAE / AE of special interest not reported in CRF within 24 hours of become aware)

The categorization of these as major deviations is not automatic and will depend on the duration and the perceived effect on efficacy.

All protocol deviations are defined in Protocol Deviation Specification document version 5.0 where a category Programmable / Observable is assigned to each deviation. Programmable deviations are programmed while Observable are checked manually during monitoring visits. Programmable deviations are then imported, and observable deviations are entered in a Protocol Deviation Tool according to classification defined in the Protocol Deviation

Specification. All deviations are then reviewed and classified on a monthly basis as Major/Minor.

A review of major protocol deviations will be performed during the data review meeting and prior to database lock, together with the lead medic, statistician and data manager.
The major protocol deviations or violations assessed to have potential impact the efficacy and safety analyses will be summarised with the pre-specified categories (refer to Protocol Deviation Specification document version 5.0).
If the number and severity of major protocol deviations which are considered to have the potential to impact the primary analysis during this review before Database lock, is considered important, sensitivity analyses may be performed. This will be decided during the data review meeting and before the database lock.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Efficacy

In this real world study tumor evaluation is per institutional standard of care, recommended to be at approximately 12 week intervals. The date of tumor assessment, method of evaluation (CT, MRI, X-ray, Ultrasound, Bone Scan, FDG-PET, Clinical examination) and the investigators opinion of the patient status (responding, stable disease, progressing) is captured in the tumor evaluation CRF.

3.1.1 **Overall Survival (OS)**

The follow-up for the patients' survival status is to be performed every 6 weeks (± 1 week) relative to the date of enrolment until end of study.
Overall survival is defined as the time from the date of first dose of AZD9291 in this study until the date of death due to any cause (i.e. date of death or censoring – date of first dose of AZD9291 in this study + 1). Any patient alive at study discontinuation will be censored at thestudy discontinuation date.

3.1.2 **Progression Free Survival (PFS)**

Progression Free Survival is defined as the time from the date of first dose of AZD9291 in this study until the date the disease is considered by the investigator to be progressing (as recorded in the tumour evaluation CRF and irrespective of the method of evaluation) or the date of death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy prior to progression (i.e. date of disease progression or death – date of first dose of AZD9291 in this study + 1). Patients who have not progressed or died at study discontinuation will be censored at the time of the latest date of disease assessment. Patients with no post baseline disease assessment will be censored at Day 1.

The PFS time will always be derived based on the date of tumour assessment or death and not visit dates.

3.1.3 **Time to Treatment Discontinuation or Death (TTD)**

As a supportive summary to PFS, time to treatment discontinuation or death will be assessed and is defined as the time from the date of the first dose of AZD9291 in the study until the date of AZD9291 discontinuation (as recorded on the discontinuation of study drug CRF) or death, regardless of the reason for discontinuation (disease progression, treatment toxicity or other reason as recorded in the CRF). This will be calculated as: date of AZD9291 discontinuation or death – date of first dose of AZD9291 + 1. Patients who transitioned to commercial supply will be censored at the date of discontinuation of study treatment (date of their last dose of study treatment).

3.1.4 **Response Rate (RR)**

Response Rate is defined as the number (%) of patients with a best response (according to investigator assessment as recorded in the tumour evaluation CRF) of 'responding', regardless of the method of evaluation, and will be based on a subset of the FAS consisting of patients with at least one documented response assessment. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of response rate. Patients who discontinue treatment without progression, receive a subsequent anti-cancer therapy and then respond will not be included as responders in the RR.

In addition, a sensitivity analysis of RR will be performed including patients who died prior to any response assessment and classifying them as non-responders.

3.2 Safety

Specified safety endpoints (Serious Adverse Events (SAEs), Adverse Events (AEs) leading to dose modification, AEs of special interest (AESIs), Hy's Law and deaths) are required to be included in the study database.

Other safety data, i.e. laboratory results (hematology, clinical chemistry and urinalysis), ECGs, and ophthalmologic assessments, are collected if performed as part of standard medical care but are not mandated in the protocol.

3.2.1 **SAEs**

SAEs will be collected throughout the study, from the date of first dose of AZD9291 until 30 days after the last dose of study medication or until disease progression, whichever is the latest. The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code the SAEs. SAEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE Version 4.03).

3.2.2 AESIs

The following AESIs will be collected and summarised:

- Interstitial lung disease/pneumonitis-like events,
- QTc prolongation events.

3.2.3 Hy's Law

Patients with potential Hy's Law criteria will be collected and summarised.

3.2.4 Duration of exposure

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

- Total exposure = (last dose date where dose > 0 mg – first dose date where dose > 0 mg + 1)/30.4375

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

- Actual exposure = (last dose date where dose > 0 mg – first dose date where dose > 0 mg + 1 – total duration of dose interruption [i.e. number of days with dose = 0 mg]) /30.4375

Note: the actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

3.2.5 Treatment Compliance

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

4 ANALYSIS METHODS

4.1 General principles

The below mentioned general principles will be followed throughout the study:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.

- For continuous data the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2

additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.

- For categorical data, percentages will be rounded to 1 decimal place.

- SAS® version 9.3 or higher will be used for all analyses.

- As the only population considered will be the FAS, all tables, listings and figures (demographics, efficacy, safety, etc.) will be provided using this population, unless indicated otherwise.

- For time interval analyses in months, duration in months will be calculated as total duration in days/30.4375

4.1.1 Handling missing data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing.

Imputation of partial dates
Initial diagnosis date:

- If year is missing (or completely missing), do not impute.
- If only day is missing, impute day as 15th of the month.
- If day and month are missing, impute as July 1st.

Concomitant medication start date

- If year is missing (or completely missing), do not impute.
- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as January 1st.
- If year and month are present and day is missing, impute day as first day of the month.

Concomitant medication end date

- If year is missing (or completely missing), do not impute.
- If (year is present and month and day are missing) or (year and day are present and month is missing, impute as December 31st.
- If year and month are present and day is missing, impute day as last day of the month.

4.2 Analysis Methods

4.2.1 Patient disposition

The total number of patients screened, enrolled and screen failed will be summarised. In addition, the number of patients in the FAS will also be provided.

The number and percentage of patients who have discontinued treatment and the main reason for discontinuation, the number and percentage of patients who transitioned to commercial

drug, as well as the number and percentage of patients who have completed or withdrawn from the study and the main reason for completion or withdrawal will be also presented.

4.2.2 **Protocol Deviations**

All identified major protocol deviations will be listed and summarised for the FAS. All protocol deviations will be defined by the study team and identified and classified as major or minor before database lock.

4.2.3 **Demographics and other baseline characteristics**

Demographic and baseline patient characteristics defined as data prior to the first AZD9291 dose (Demography, Receptor status, Lung cancer disease characteristics, Evaluation of brain/leptomeningeal metastases, which may be based on a scan taken within 28 days after the first dose (Please note: the delayed baseline assessment may introduce errors in the reported number of patients with brain/leptomeningeal metastases at baseline due to an early response to the treatment, or early progression in the site of brain/leptomeningeal.), Previous cancer therapy, Weight, WHO performance status, Electrocardiogram, Ophthalmologic assessment) will be summarised for the FAS.

In addition, the number (%) of patients by country of enrolment and by race (Asian vs non-Asian) will be summarised.

For receptor status the number (%) of patients positive for T790M only, the number (%) of patients positive for T790M + 1 other mutation, the number (%) of patients positive for T790M + 2 other mutations, the number (%) of patients positive for T790M + 3 other mutations, the number (%) of patients positive for T790M + 4 other mutations and the number (%) of patients positive for T790M + 5 other mutations will be summarised.
Specific mutation combinations will also be summarised.
In addition, the following subgroups will be identified and number (%) for each subgroup will be summarised:

- T790M only
- Common mutations: T790M + Exon 19 Deletion only
  T790M +L858R only
- Uncommon/ Compound mutations:
  - Uncommon mutation T790M + G719X only
    T790M + S768I only
    T790M + Exon 20 Insertion only
  - Common compound mutations: T790M + 2 common mutations
  - Uncommon compound mutations: T790M + 2 or more mutations including at least 1 uncommon mutation

In this analysis patients classified as not detected or not done for a particular mutation will be regarded as not having the mutation.

Receptor status will also be summarised by brain/leptomeningeal metastases status at screening (Present; Absent, Not Done), by sample type (Plasma; Tissue; Other) and by prior

type of therapy (TKI alone; TKI + Other anti-cancer therapy including any anti-cancer treatment other than a TKI, palliative radiotherapies and surgery associated with advanced lung cancer as defined in Appendix 6).

Previous anti-cancer treatments will be summarised by category: TKI, Chemotherapy, Immunotherapy, Antiangiogenic therapy, Other anti-cancer treatment.
Lists of possible TKIs, Chemotherapy agents, Immunotherapy agents and Antiangiogenic therapies are provided in Section 9. All other anti-cancer treatments that are not listed in Section 9 are considered in the Other therapies category.

Previous radiotherapies and previous surgeries will also be summarised.
Previous surgeries will be summarised by category: associated with advanced lung cancer: not associated with advanced lung cancer.
List of surgeries associated with advanced lung cancer is provided in Section 9. All other surgeries not listed in Section 9 are considered as not associated with advanced lung cancer.

Additionally, the following derived variables will be summarised:

- Age at study enrolment as a continuous variable
- Age at study enrolment by class (<50; >=50 - <65; >=65 - <75; >=75 - <80,>=80 and <65; >=65)
- Duration from most recent receptor status assessment for T790M mutation to study enrolment (months)
- Duration from original lung cancer disease diagnosis to study enrolment (months)
- Duration from last TKI exposure to study enrolment (<= 6 months, > 6 months)
- Duration from last dose of prior cancer therapy to study enrolment (months)
- Duration from scan for evaluation of brain/leptomeningeal metastases to study enrolment (months)
- Duration from last dose of prior anti-cancer therapy to most recent receptor status for T790M mutation (months)

Enrolment date corresponds to the date enrolment ID and AZD9291 are allocated to the subject in Interactive Web Response System (IWRS). Enrolment date may be prior to first dose date of AZD9291.

4.2.4 **Medical History**

Relevant medical history (past and current) and relevant surgical history will be coded using the latest version of MedDRA.

All medical history will be summarised (number and percentage of patients) for the FAS by system organ class (SOC) and preferred term (PT).

All relevant surgical history will be summarised similarly.

4.2.5 Concomitant Medication / Treatment

Concomitant medications are those with a stop date on or after the first dose date of study treatment or those that are marked as ongoing (and could have started prior to or during treatment).
Concomitant medication / treatment will be summarised using frequency tables by anatomical therapeutic chemical classification (ATC) code.

4.2.6 Exposure and Compliance to AZD9291

Exposure (total and actual) to AZD9291 will be summarised in months for the FAS and for discontinued patients as a continuous variable and by class (<3; [3-6[; [6-12[; [12-18[; >=18 months).

Total Exposure Plot
A plot giving the decreasing percentage of patients still on treatment against time (months) will be presented.

Compliance
Treatment compliance is calculated as the proportion in percentage of the scheduled expected number of doses, i.e. (Actual exposure/Total exposure)*100.

Compliance will be summarised as a continuous variable for the FAS.

4.2.7 Efficacy

Overall Survival (OS)
Overall survival will be summarised using Kaplan-Meier (KM) estimates of the median time to death or censoring and quartiles together with their 95% confidence intervals. Kaplan-Meier estimates of the OS rate at appropriate time points (see Event rate at fixed time point) will be presented as well.

A plot of the KM OS curve will be produced, including tickmarks to identify censored observations and numbers of patients at risk.

The number of patients prematurely censored will be summarised. A patient would be defined as prematurely censored if moving to commercial supply or if their survival status was not defined at the date of study discontinuation and if his/her last available information in the CRF is more than 6 weeks prior to the study discontinuation.

In addition, duration of follow-up will be summarised:

- In censored patients who are alive at the last assessment before study discontinuation only: Time from date of first dose of AZD9291 in this study to date of censoring (date last known to be alive).
- In prematurely censored patients: Time from date of first dose of AZD9291 in this study to date of censoring.

- In all patients: Time from date of first dose of AZD9291 in this study to the date of death (i.e. overall survival) or to the date of censoring for censored patients.

Progression Free Survival (PFS)
Progression Free Survival will be summarised similarly to OS using Kaplan-Meier (KM) estimates of the median time to progression or death (by any cause in the absence of progression) and quartiles together with their 95% confidence intervals. KM estimates of the PFS rate at appropriate time points (see Event rates at fixed time points) will be presented as well.

Progression free survival events will be divided into 3 categories: Progression, Death due to disease progression, and Death due to reasons other than disease progression. Patients who have a progression event recorded in the tumor evaluation CRF will be summarised under 'Progression'. Patients with no progression event recorded in the tumor evaluation CRF but who have died with the cause of death assessed as due to disease progression as per list defined in appendix 5 will be summarised under 'Death due to disease progression', and patients who have died due to other causes will be summarised under 'Death due to reasons other than disease progression'.

Patients who have no progression or death record entered into the relevant CRF will be censored as described in section 3.1.2.

A plot of the KM PFS curve will be produced, including tickmarks to identify censored observations and numbers of patients at risks at each specific fixed time points (see Event Rates at Fixed Time Points).

The treatment status on the date of progression/death or censoring of patients will be summarised.
This will include the number (%) of patients who were on treatment at the time of progression, the number (%) of patients who discontinued study treatment prior to progression, the number (%) of patients who had not progressed and were on treatment or discontinued treatment at time of censoring.

Additionally, the number (%) of patients who continue on study treatment after progression will be summarised.
Patients are considered as continuing treatment after progression if stop date is more than 7 days after progression date.

Time to Treatment Discontinuation or Death (TTD)
As for OS, Time to Treatment Discontinuation or death will be summarised using Kaplan-Meier (KM) estimates of the median time to treatment discontinuation or death and quartiles together with their 95% confidence intervals. KM estimates of the rate of patients still on treatment at appropriate time points (see Event Rates at Fixed Time Points) will be presented as well.

A plot of the KM estimates of TTD will be produced, including tickmarks to identify censored observations and numbers of patients at risks at each time point.

Event Rates at Fixed Time Points

For OS, PFS and TTD, event rates will be presented at specific fixed time points.
Initially an interval of 3 months will be chosen extended to 6 months after 18 months: 3, 6, 9, 12, 15, 18, 24, 30, 36 months, but this may be adjusted appropriately according to the distribution of the time-to-event variable and follow-up time.

Response Rate

Response rate, as defined in Section 3.1.4, will be summarised together with exact 95% confidence interval using the Clopper-Pearson method, based on a subset of the FAS consisting of patients with at least one documented response assessment.
The Best Overall Response (responding, stable disease, progressing, not evaluated) will also be summarised.
A sensitivity analysis of response rate will also be performed including patients who died prior to any documented response assessment and classifying them as non-responders.

Evaluation of Brain/Leptomeningeal Metastases at Progression (regardless of site of progression)

Brain/leptomeningeal metastases at progression (***regardless of site of progression)*** will be summarised separately for patients with presence and absence of brain/leptomeningeal metastases at screening for patients who have a baseline assessment of brain/leptomeningeal metastases:

- For patients without brain/leptomeningeal metastases at screening, the method of assessment, presence of a lesion at progression and sites of lesions (Brain/Leptomeningeal) will be summarised.
- For patients with brain/leptomeningeal metastases at screening, the method of assessment and status at progression will be summarised.

Subgroup Analyses

Demographics, OS, PFS, TTD and RR will be analysed in the following subgroups of the FAS:

Subgroup	Demo-graphics	OS	PFS	TTD	RR
• Sex (male ; female)	√	√	√	√	√
• Age at enrolment (<75 ; ≥75 years of age)	√	Summary of cause of death	√	√	√
• Race (White, Black, Asian, and Other).	√		√	√	√
• Ethnicity (Asian, non-Asian).	√	√	√	√	√
• Country of enrolment	√		√	√	√
• WHO Performance Status (<2; =2)	√	√	√	√	√

Subgroup	Demo-graphics	OS	PFS	TTD	RR
• Prior Lines of therapy (one line ; more than one line)	√		√	√	√
• Mutation combinations as defined in section 4.2.3: (T790M only ;Common mutations Uncommon / Compound mutations)	√		√	√	√
• Mutation Status (Any compound mutations with a sample size of at least 50 patients (n≥50))	√		√	√	√
• Sample Type for receptor status assessment (Plasma ; Tissue ; Other)	√	√	√	√	√
• Type of T790M testing (Roche cobas® test on plasma ; Every other test on plasma with at least 50 patients ; Roche cobas® test on tissue ; Every other test on tissue with at least 50 patients)	√		√	√	√
• Brain/leptomeningeal metastases status at baseline (Present ; Absent ; Not Done)	√	√	√	√	√
○ Prior radiotherapy (Y/N) in Brain/leptomeningeal metastases subgroup	√		√		√
• Prior Type of anti-cancer therapy (TKI alone[1] ; TKI + Other anti-cancer therapy[2]))	√	√	√	√	√
• Prior Type of TKI (TKI first generation only ; TKI second generation only ; TKI first generation + TKI second generation, TKI first generation and/or second generation + TKI third generation)	√		√	√	√
• Prior chemotherapy (Yes [3; No)	√	√	√	√	√
○ Line of Chemotherapy (First line; Second line; Third line or more)	√		√	√	√

[1]TKI alone does not refer to monotherapy, but only ever having previously received a TKI and no other anti-cancer treatment in the metastatic setting.
[2] Other anti-cancer therapy includes any anti-cancer treatment other than a TKI, palliative radiotherapies and surgery associated with advanced lung cancer as defined in Appendix 6.
[3] Subgroup Prior chemotherapy = Yes includes all patients previously treated by chemotherapy other than adjuvant or neo-adjuvant only.

Subgroup	Demo-graphics	OS	PFS	TTD	RR
• Use of TKI in patients with prior first or second line chemotherapy (Yes; No)	√		√	√	√

The subgroup analyses will be based on the values recorded on the CRF.

The subgroup analyses for time-to-event endpoints will be performed only for the subgroups with 20 events or more.

The summary of cause of death by age class will include disease under study, AEs not considered related to AZD9291, AEs considered related to AZD9291, Other.
Deaths due to disease under study are defined as deaths due to disease progression as defined in the list in Appendix 5.

A swimmer plot for PFS will be produced for the uncommon/compound mutation subgroup and a listing of PFS for patients with T790M + Exon 20 Insertion only will be presented.

4.2.8 **Safety**

Serious Adverse Events (SAE)
All SAEs starting after the first dose of therapy, or within 30 days after stopping therapy, will be included in the summary table providing frequency (the same SAE occurring more than once to the same patient will be taken into account only once).
SAEs will be presented by System Organ Class (SOC) and Preferred Term (PT).
SAEs leading to death and SAEs leading to treatment discontinuation will be also summarised separately.

Any SAEs occurring before starting treatment with AZD9291 will be included in the data listing but will not be included in the summary tables of SAEs.

Adverse Events of Special Interest (AESI)
Summaries of the AESIs will include number (%) of patients who have:

- At least one AESI
- At least one AESI related to study medication. If causality is missing, assume that the AESI is related.
- At least one AESI leading to dose modification (reduction/interruption)
- At least one AESI leading to discontinuation

A summary of duration (days) of AESI will be provided for all events and this will be supported by summaries of events which have an end date, ongoing AESIs at death and, separately, at study discontinuation. All durations will be calculated.
Duration of Ongoing AESIs will be calculated using study discontinuation date as end date.

Duration of fatal AESIs will be calculated using death date collected on death form as end date.

Summary statistics of Time of Onset (days) from study treatment to start of AESI will also be provided for all AESIs.

Summary tables of AESIs providing the number (%) of patients experiencing any of the specified terms by maximum CTCAE grade will be also produced.

AEs leading to dose modification
AEs leading to dose modification (reduction/interruption) will be presented by SOC and PT.

AEs leading to discontinuation
AEs leading to discontinuation will be presented by SOC and PT.

Deaths
A summary of deaths and cause of death will be provided and a corresponding listing will also be produced.

An overall summary of AEs will be presented including:
Number (%) of patients with at least one AE, number (%) of patients with at least one AE leading to dose modification, number (%) of patients with at least one AE leading to discontinuation, number (%) of patients with at least one AESI, number (%) of patients with at least one SAE.

Subgroup analyses
Overall summary of AEs will be analysed in the following subgroups of the FAS:

- Age at enrolment (<75 ; ≥75 years of age)
- Baseline WHO Performance Status (<2; =2)
- Sample Type (Plasma ; Tissue ; Other)
- Brain/leptomeningeal metastases status at baseline (Present ; Absent ; Not Done)

4.2.9 Laboratory evaluations

When laboratory parameters are collected, they will be assessed by the investigator as normal, abnormal-not clinically significant, abnormal-clinically significant, abnormal-leading to dose modification or abnormal-SAE. Details about abnormality will be summarised in tables by parameter and visit.

4.2.10 ECG

QTc interval fredericia >470 ms (Yes, No), overall evaluation (Normal, Abnormal) and clinically significance (Yes, No) will be summarised by visit.

4.2.11 **Weight**

Weight (Kg) will be summarised by visit.

4.2.12 **WHO performance status**

WHO performance status (Normal Activity, Restricted Activity, In Bed Less Than or Equal to 50% of the Time, In Bed More Than 50% of the Time, 100% Bedridden, Death) will be summarised by visit.

4.2.13 **Slit Lamp Test)**

Slit Lamp test results (Normal, Abnormal) will be summarised by left and right eyes and by visit.

5 INTERIM ANALYSES

To provide annual updates of key study measures, interim analyses of the global data will take place annually for the first three years (i.e. at approximately 12, 24 and 36 months from the start of recruitment).

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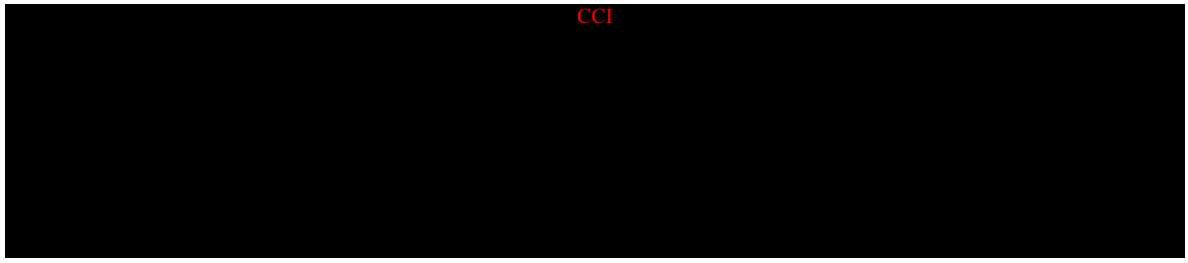

6 CHANGES OF ANALYSIS FROM PROTOCOL

N.A

7 COUNTRY SPECIFIC ANALYSES

Regional and country level analysis may be performed at the interim analyses and final analysis time points if deemed appropriate.
KM OS analysis and outputs will only be presented for countries that have enrolled a minimum of 150 patients and have at least 60% event maturity to ensure robustness of data for this endpoint.

8 REFERENCES

Clopper, C. J. & Pearson, E. S., 1934. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika,* Volume 26, pp. 404-413.
Collett, D., 1994. *Modelling Survival Data in Medical Research.* s.l.:Chapman & Hall/CRC.

9 APPENDICES

1. List of Tyrosine kinase inhibitors

Preferred Name	Generation
AZD3759	1st generation
Gefitinib	1st generation
Epitinib	1st generation
Erlotinib	1st generation
Icotinib	1st generation
Afatinib	2nd generation
Dacomitinib	2nd generation
Poziotinib	2nd generation
EGF816/Nazartinib	3rd generation
Avitinib	3rd generation
Olmutinib	3rd generation
Osimertinib	3rd generation
Rociletinib	3rd generation

2. List of Chemotherapies:

Preferred Name
Bleomycin
Capecitabine
Carboplatin
Carmustine
Cisplatin
Cytarabine
Docetaxel
Doxorubicin
Epirubicin
Etoposide
Fluorouracil
Gemcitabine
Gimeracil
Ifosfamide
Irinotecan
Lobaplatin
Nedaplatin
Nimustine
Olaparib
Oteracil
Oxaliplatin
Paclitaxel
Pemetrexed
Platinum compounds
Tegafur
Temozolomide
Teniposide
Uftoral
Vincristine
Vinorelbine
Vorinostat

3. List of Immunotherapies:

Preferred Name
Atezolizumab
Avelumab
Durvalumab
Ipilimumab
Nivolumab
Pembrolizumab
Tremelimumab

4. List of Antiangiogenic Therapies:

Preferred Name
Anlotinib
Apatinib
Endostatin
Bevacizumab
Fruquintinib
Nintedanib
Ramucirumab
Telatinib

5. Death due to disease progression coded terms:

Coded term
Adenocarcinoma of lung
Advanced cancer
Brain metastases
Cancer
Cancer of lung
Disease aggravation
Disease progression
Lung adenocarcinoma
Lung cancer
Lung cancer metastatic
Lung neoplasm
Malignant neoplasm of lower lobe, bronchus or lung, in situ
Meningeal carcinomatosis
Non-small cell lung cancer
Non-small cell lung cancer metastatic
Progression of non-small cell lung cancer
Tumor progression

6. Surgeries associated with advanced lung cancer:

Preferred term
Lung lobectomy
Lymphadenectomy
Pulmonary resection
Lung neoplasm surgery
Pneumonectomy
Brain tumour operation
Pleurectomy
Hepatectomy
Adrenalectomy
Bone lesion excision
Vertebroplasty
Brain lobectomy
Internal fixation of spine
Lymphoid tissue operation
Metastases to central nervous system
Pericardial drainage
Pericardial effusion malignant
Pleural adhesion
Pleural decortication
spinal corpectomy
Spinal decompression
Tracheal resection
Tumour excision
Ventriculo-pleural shunt

- **Protocol number:** D5160C00022
- **Document title:** Open Label, Multinational, Multicenter, Real World Treatment Study of Single Agent AZD9291 for Patients with Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Prior Therapy with an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI).
- **Version numbers:** SAP Addendum Version 1.0
- **Date of the documents:** 03 Nov 2020
- **NCT number:** NCT02474355

Real World Treatment Study – Statistical Analysis Plan (for the final analysis) – Addendum 01

Drug Substance	AZD9291
Study Code	D5160C00022
Version Number	1.0
Date	03 November 2020

Open Label, Multinational, Multicenter, Real World Treatment Study of Single Agent AZD9291 for Patients with Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Prior Therapy with an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

SIGNATURE PAGE

Open Label, Multinational, Multicenter, Real World Treatment Study of Single Agent AZD9291 for Patients with Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Prior Therapy with an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI)

Global Product Statistician	PPD	PPD

SIGNATURE PAGE

Open Label, Multinational, Multicenter, Real World Treatment Study of Single Agent AZD9291 for Patients with Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Prior Therapy with an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI)

Study Statistician	PPD	PPD

SIGNATURE PAGE

Open Label, Multinational, Multicenter, Real World Treatment Study of Single Agent AZD9291 for Patients with Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Prior Therapy with an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI)

Parexel Senior Biostatistician PPD PPD

TABLE OF CONTENTS

AMENDMENT HISTORY

Category: Change refers to	Date	Description of change	In line with CSP? Y (version) / N / NA	Rationale
Efficacy	16 Apr 2020	Add OS swimmer plot for uncommon/compound mutation subgroup	NA	Subgroup of interest for OS
Safety	19 Jun 2020	Add table of AEs with CTCAE Grade >=3 Add Table of AESIs by outcome Add Table of SAE by causality Add Table of SAE by CTCAE grade Update Table of Hy's Law cases Add Listing of SAEs Add Listing of AESIs Add Listing of Hy's Law cases	NA	Adverse events analysis needs more details
	09 Oct 2020	Add Summary of Serious Adverse Events Leading to Dose Modification by System Organ Class and Preferred Term	NA	

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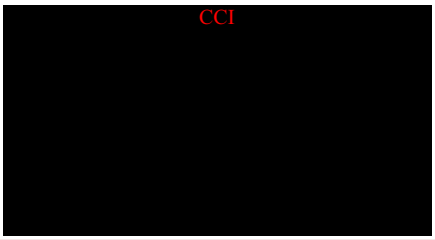

Appendices	16 Apr 2020	Recoding of Telatinib in antiangiogenic therapies	NA	Dictionaries updated

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BICR	Blinded Independent Central Review
BOR	Best Objective Response
CTCAE	National Cancer Institute Common Terminology Criteria for AEs
DoR	Duration of Response
FAS	Full Analysis Set
ORR	Objective Response Rate
OS	Overall Survival
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TBL	Total Bilirubin
ULN	Upper Limit of Normal

1 STUDY DETAILS

This Statistical Analysis Plan (SAP) addendum outlines additional outputs and appendices updates after SAP final version 7.0.

2 ANALYSIS SETS

2.1 Definition of analysis set

Full Analysis Set (FAS)
The full analysis set is defined the same way as detailed in Section 2.1 of the SAP.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Efficacy

3.1.1 Overall Survival (OS)

Overall survival is defined the same way as detailed in Section 3 of the SAP.

3.2 Safety

3.2.1 Serious Adverse Events (SAEs)

SAEs are defined the same way as detailed in Section 3 of the SAP.

3.2.2 Adverse Events of Special Interest (AESIs)

AESIs are defined the same way as detailed in Section 3 of the SAP.

4 ANALYSIS METHODS

4.1.1 Efficacy

Overall Survival (OS)
Overall survival will be summarised by mutation combination subgroup.
Analysis will include the number of exposed patients, the number of deaths, the number of censored patients and the number of patients prematurely censored.
In addition, duration of follow-up will be summarised as defined in Section 4.2.7 of the SAP:

- In all censored patients;
- In prematurely censored patients;
- In all patients.

A swimmer plot for OS will be produced for the uncommon/compound mutation subgroup. The swimmer plot will include all patients with an uncommon/compound mutation and will be ordered by mutation combination. Median OS and 95% confidence intervals for Full Analysis

Set will be reported as reference lines. Censored patients will be identified by a cross at the time of censoring.

4.1.2 Safety

All the following outputs will be provided in addition to analyses described in Safety analysis methods section of the SAP (Section 4.2.8).

Serious Adverse Events (SAE)
The following summaries will be provided for all SAEs as defined in the SAP section 4.2.8:

- number (%) of patients reporting SAEs assessed as causally related to AZD9291 by System Organ Class (SOC) and Preferred Term (PT). If causality is missing, assume that the SAE is causally related.
- number (%) of patients reporting SAEs by SOC, PT and maximum CTCAE grade.
- number (%) of patients reporting SAEs leading to dose modification by SOC and PT.

A listing of all SAEs will be produced. SAEs occurring before starting treatment with AZD9291 included in the data listing will not be included in the summary tables of SAEs.

Adverse Events of Special Interest (AESI)
Summary table of AESIs providing the number (%) of patients experiencing any of the specified terms by outcome will be produced.

A listing of all AESI will also be produced.

The overall summary described in SAP section 4.2.8 will be replaced by an overall summary of AESIs and SAEs including:

- number (%) of patients with at least one AESI or SAE
- number (%) of patients with at least one AESI or SAE causally related to AZD9291
- number (%) of patients with at least one AE leading to dose modification
- number (%) of patients with at least one AE leading to discontinuation
- number (%) of patients with at least one AESI
- number (%) of patients with at least one AESI causally related to AZD9291
- number (%) of patients with at least one SAE.
- number (%) of patients with at least one SAE causally related to AZD9291
- number (%) of patients with at least one AE leading to death
- number (%) of patients with at least one AE leading to death causally related to AZD9291

Note: If causality is missing, assume that the AE is causally related.
Subgroup analyses
Overall summary of AESIs and SAEs will be analysed in all subgroups of the FAS as defined in section 4.2.8 of the SAP.

A summary table of AEs with CTCAE grade ≥ 3 providing the number (%) of patients experiencing any of the specified terms will be also produced.

4.1.3 **Potential Hy's Law cases**

A cross tabulation of number (%) of patients who had any instance of an elevated aspartate transaminase / alanine transaminase (AST or ALT ≥ 3xULN) with number (%) of patients who had any instance of elevated total bilirubin (TBL ≥ 2xULN) will be presented in order to evaluate potential Hy's Law cases.

Potential Hy's Law cases will also be presented in a listing.

5 INTERIM ANALYSES

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6 CHANGES OF ANALYSIS FROM PROTOCOL

NA

7 APPENDICES

1. List of Tyrosine kinase inhibitors

The following list replaces the list provided in Section 9 of the SAP.

Preferred Name	Generation
AZD3759	1st generation
Gefitinib	1st generation
Epitinib	1st generation
Erlotinib	1st generation
Icotinib	1st generation
Afatinib	2nd generation
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Theliatinib	2nd generation
EGF816/Nazartinib	3rd generation
Avitinib	3rd generation
Olmutinib	3rd generation
Osimertinib	3rd generation
Rociletinib	3rd generation

2. List of Chemotherapies:

Refer to Section 9 of the SAP

3. List of Immunotherapies:

Refer to Section 9 of the SAP

4. List of Antiangiogenic Therapies:

Refer to Section 9 of the SAP

5. Death due to disease progression coded terms:

Refer to Section 9 of the SAP

6. Surgeries associated with advanced lung cancer:

Refer to Section 9 of the SAP