- **Protocol number:** D5160C00007.
- **Document title:** A Phase III, Double-Blind, Randomised Study to Assess the Efficacy and Safety of AZD9291 versus a Standard of Care Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor as First-Line Treatment in Patients with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer.
- **Version number: 4**.0.
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Clinical Study Protocol	
Drug Substance	AZD9291
Study Code	D5160C00007
Version Number	4.0
Date	7 March 2018

A Phase III, Double-Blind, Randomised Study to Assess the Efficacy and Safety of AZD9291 versus a Standard of Care Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor as First-Line Treatment in Patients with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

EudraCT number: 2014-002694-11

VERSION HISTORY

Version 4.0 2 March 2018

Changes to the protocol are summarized below:

The primary reason for amending this protocol is to:

- Outline patient management post primary PFS analysis and post final OS analysis (at approximately 60% maturity)
- Update to reflect changes in the current Investigator's Brochure (IB) regarding the management of toxicities

In addition, the protocol has been converted to the newest AstraZeneca protocol template. For this, the following changes have occurred:

- All appendices are now part of the main body
- Removal of signature lines and references to amendment and administrative changes as details have now been moved into the version history section

The primary, secondary and exploratory objectives of this protocol remain unchanged. Recruitment into the study is complete, the DCO date for the primary objective for the study (PFS analysis) was 12th June 2017, and the analysis reported concluded a positive result for the study. A clinically meaningful and statistically significant result was observed for the primary objective, PFS, and supporting evidence was also observed for other primary, secondary, and exploratory objectives. No inclusion or exclusion criteria were amended.

Major changes to the protocol are summarised below:

Section Protocol Synopis (International Co-ordinating Investigator):

Updating the list of International Co-ordinating Investigator (ICI) by removing Professor Jean-Charles Soria, M.D., Ph.D. as he terminated his service from Institut Gustave Roussy and thus the of role of ICI for study D5160C00007.

1.4 (Study design): Added clarity on tumour assessment requirements post global primary PFS analysis and for China cohort PFS analysis.

Section 3.7 (Methods for unblinding), Section 3.9.1 (Procedures for discontinuation of a patient from investigational product), Section 5 (Study Assessments), Section 6.1 (Definition of adverse events), Section 7.4 (Storage), Section 7.6 (Accountability), Section 9.2.1 (Source data), Section 9.2.2 (Study agreements), Section 9.2.3 (Archiving of study

documents), Section 9.3 (Study timetable and end of study), Section 10.1 (Ethical conduct of the study), Section 10.2 (Patient data protection), Section 10.3 (Ethics and regulatory review), Section 10.4 (Informed consent), Section 10.5 (Changes to the protocol and informed consent) and Section 10.6 (Audits and inspections): Removal of template guidance text for Japan that was not removed prior to finalization of the clinical study protocol. Any specific Japan requirements are managed via local Japan protocol amendments.

Section 3.8 (Restrictions): Updated the length of time for male and female patients that reliable methods of contraception should be used post discontinuation of study treatment and updated the restrictions on male patient regarding sperm donation. In addition, removal of restrictions on statin use, INR monitoring and use of contact lenses. These changes are to align with the latest version of the Investigator Brochure.

Section 3.9 (Discontinuation from investigational product): addition of QTc interval prolongation with signs and symptoms of serious arrhythmia as criteria for not restarting study treatment and removal of corneal ulceration as criteria for not restarting study treatment which aligns with updated Tagrisso Investigator Brochure content.

Section 4 (Study Plan and timing of procedures) – Table 1 Study plan (up to Primary PFS Analysis for Global Patients and up to China PFS Analysis for China Cohort): Updated Table 1 label to clarify it outlines procedures for patients prior to Primary PFS analysis. Addition of Footnote "p" to clarify ECG collection requirement at 28-day Follow-up Visit.

Section 4 (Study Plan and timing of procedures) – Table 2 Study plan for post-progression cross-over to AZD9291 from SoC treatment arm up to Primary PFS Analysis: Updated Table 2 label to clarify it outlines procedures for cross-over patients prior to Primary PFS analysis. Added Subsequent response/progression data collection during Survival Follow-up Visits as this was an omission in prior protocol version. Addition of Footnote "h" to clarify subsequent response/ progression is based on investigator assessment.

Section 4 (Study Plan and timing of procedures) – Table 3 Study Schedule Post Primary PFS Analysis and up to the Final OS Analysis: Addition of a new Study Plan Table to provide guidance on patient procedures and timings after Primary PFS analysis and up to the Final OS analysis.

Section 4.4 (Patient management post primary PFS analysis and up to final OS analysis): Section added to provide more detail regarding the management of patients post primary PFS analysis and up to the final OS analysis data cut-off.

Section 4.5 (Patient management post final OS analysis): Section added to provide more detail on the management of patients after completion of the final OS analysis.

Section 5.1.1 (RECIST v1.1 up to Primary PFS analysis) and Section 5.1.2 (RECIST version 1.1 assessment of Blinded Independent Central Review): Additional text added to

clarify tumour assessments following the primary PFS analysis including differences for the China Cohort.

Section 5.2.3 (Electrocardiogram): Addition of text outlining the change from central ECG collection & evaluation to local ECG collection & evaluation following primary PFS analysis, China PFS analysis.

Section 5.2.4 (Patient Reported Outcomes): Addition of text outlining the change of collection regarding Patient Reported Outcomes. Patient Reported Outcomes will not be collected post PFS analysis

Section 5.7.3 (Collection of plasma samples for analysis: blood-borne biomarkers and circulating deoxyribonucleic acid): Clarification text added for collection post primary PFS analysis.

Section 6.3.1 (Time period for collection of adverse events in the eCRF): New text added to outline collection of AEs following the final OS analysis.

Section 6.3.9 (Disease under study): Section was modified to align the CSP with updated internal AstraZeneca protocol standards.

Section 6.4 (Reporting of serious adverse events): Additional text added to document the closure of the web based data collection system following the final OS analysis and guidance for reporting SAE for patients who continue on study medication.

Section 6.5 (Overdose): Statement added to clarify that a maximum tolerated dose of AZD9291 has not been established.

Section 6.6 (Pregnancy): Section was modified to reflect the current Investigator's Brochure (IB) update to timelines for reporting of pregnancies and outcome.

Section 6.6.2 (Paternal exposure): Section was modified to reflect the current Investigator's Brochure (IB) update to timelines for reporting of pregnancies outcome.

Section 6.7 (Management of Investigation Product-related Toxicities): Updated with guidelines for dose adjustments to reflect the current Investigator's Brochure (IB)

Section 6.7.3 (Interstitial Lung Disease): Updated to include changes from Administrative change 2 dated July 6th 2016.

Section 6.7.6 (Keratitis): New section added with guidelines for Keratitis to reflect the current Investigator's Brochure (IB).

Section 7.2 (Dose and Treatment regimens): Section updated to include details on how

drug dispensing will occur post final Overall Survival analysis.

Section 7.5 (Compliance): Section updated to include details on drug accountability requirements post final Overall Survival analysis.

Section 7.8 (Post-study access to study drug): Section updated to include information on access to AZD9291 post final Overall Survival analysis.

Section 8.1 (Statistical Considerations): Multiple testing strategy updated in line with the latest version of the FLAURA SAP.

Section 8.5.2.1 (Hierarchical testing of key secondary variables): Testing strategy updated in line with the latest version of the FLAURA SAP.

Section 8.4.1 (Calculation or derivation of efficacy variables): Added detail for the MMRM modelling for the 5 key PRO items Dyspnoea, Cough, Pain in Chest, Fatigue, and Appetite Loss.

Section 8.5.2.3 (Analysis of Overall Survival): Added clarity around the timing of the final OS analysis for the China cohort.

Section 8.6 (Post primary PFS – global cohort): Section added to describe changes in data collection and analysis following primary PFS DCO, and what will be presented at the final OS analysis.

Section 8.8 (Post China primary PFS – China cohort): Section added to describe changes in data collection and analysis following primary PFS DCO, and what will be presented at the final China OS analysis

Section 10.5 (Changes to the protocol and informed consent form): Section updated to outline new process for changes to the clinical study protocol.

Appendix B (Guidance Regarding Potential Interactions with Concomitant Medications): Updated per the latest version of the Tagrisso (AZD9291) drug-drug interaction appendix

Appendix I (Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods): New appendix added to outline acceptable contraceptive methods in more detail.

Version 3.0 24th September 2015

Changes to the protocol are summarized in Amendment 2 (dated 24-Sep-2015) and

administrative change 1 (dated 23-Jul-2015).

Version 2.0 13th April 2015 Changes to the protocol are summarized in Amendment 1.

Version 1.0 8th August 2014 Initial Document

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

A Phase III, Double-Blind, Randomised Study to Assess the Efficacy and Safety of AZD9291 versus a Standard of Care Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor as First-Line Treatment in Patients with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

International Co-ordinating Investigator:

PPD, **M.D.**
Professor of Hematology and Medical Oncology Director
Division of Medical Oncology
Emory University, Winship Cancer Institute
Atlanta, Georgia, USA

Study sites and number of patients planned

Approximately 220 sites across Asia, Europe, North America, and South America will randomise approximately 530 patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC). Once 530 patients have been recruited globally, recruitment may continue in mainland China only until approximately 120 patients have been recruited in total in China.

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2014	III
Estimated date of last patient completed globally	Q2 2019	

Study design

This is a Phase III, double-blind, randomised study assessing the efficacy and safety of AZD9291 (80 mg orally, once daily) versus a standard of care (SoC) Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) (either gefitinib [250 mg orally, once daily] or erlotinib [150 mg orally, once daily]) in patients with locally advanced or metastatic EGFR sensitizing mutation (EGFRm+) Non-small Cell Lung Cancer (NSCLC) who are treatment-naïve and eligible for first-line treatment with an EGFR-TKI.

In order to randomise approximately 530 patients, it is estimated that 980 patients will be screened. Patients will be stratified by mutation status (exon 19-deletion [Ex19del] or exon 21 [L858R] substitution) and race (Asian versus Non-Asian).

Once 530 patients have been recruited globally, recruitment will continue in mainland China only until approximately 120 patients have been recruited in China. This is to ensure adequate Chinese patient participation to satisfy China FDA requirements and in order to provide an opportunity for a safety and efficacy assessment of AZD9291 in Chinese patients with locally advanced or metastatic EGFRm+ NSCLC. It is anticipated that this may not be met before the global recruitment target of 530 is achieved.

Enrolment completed in Mar 2016 for the Global cohort (556 pts recruited including 19 in China). Recruitment completed in Jun 2017 in China and a further 117 patients were recruited. All 136 patients enrolled in China will be referred to as the China Cohort and will be included in the China analysis and reported in separated CSR.

Note: Sites will be required to select either gefitinib or erlotinib as the sole comparator prior to site initiation (with the exception of the United States of America [USA, where all sites will use erlotinib] and Japan [where all sites will use gefitinib]). The selected SoC EGFR-TKI will be used in accordance with the marketing authorisation for the country.

Eligible patients will be randomised to receive either AZD9291 or SoC EGFR-TKI (gefitinib or erlotinib) in a 1:1 ratio. Patients should continue on their randomised treatment until Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) defined progression or until a treatment discontinuation criterion is met. However, if patients continue to show clinical benefit to treatment as judged by the Investigator, patient may continue to receive their randomised treatment beyond RECIST v1.1 defined progression. Therefore, there is no maximum duration of treatment. Up to the primary PFS analysis, subjects must be followed until evidence of RECIST 1.1 defined progression (regardless of reason for treatment discontinuation). It is important that patients are assessed according to the intended scanning schedule to prevent the bias in analysis that can occur if one treatment group is assessed more or less often than the other. Tumour assessments according to RECIST v1.1 are to be performed every 6 weeks (± 1 week) relative to randomisation until objective disease progression or as per standard practice post progression. Patients will be followed for survival every 6 weeks following objective disease progression. Tumour assessments are to be performed every 12 weeks (+/- 1 week) for patients on study treatment >=18 months following randomisation.

Following objective disease progression according to RECIST 1.1, as per investigator assessment, patients who were randomized to SoC arm may have the option to receive open-label AZD9291 provided the following criteria are met, and should the patient wish to do-so:

- Disease progression confirmed by independent central imaging review which must be established prior to a patient being unblinded. (Note, if central confirmation of progression is not confirmed, the patient is not eligible to receive open-label AZD9291 at that time. Should it be in the patients best interests, they may continue to receive randomized treatment and submit the next scan for central imaging review according to the study schedule.)

- the patient cannot cross-over if they have received intervening therapy following discontinuation of randomized treatment

- tumour confirmed as T790M mutation positive following disease progression (may be determined before or after a patient has been unblinded.)

Provided the above criteria have been met, and the patient was randomized to the SoC treatment arm, the patient may commence open-label AZD9291. If the patient has been unblinded and they are not eligible for crossover or choose not to crossover, they cannot recommence or continue on their randomized treatment. See Section 4.3.5 for further details on post-progression cross-over to AZD9291

Following the final global OS analysis, the FLAURA study will be closed, and the collection of survival and safety data for globally recruited patients no longer on study treatment will stop entirely. Those patients still benefiting from study drug will be managed through the Post Analysis & Reporting Team (PART) within AstraZeneca. Data will continue to be collected in patients recruited in mainland China until the final Chinese OS analysis if this occurs later than the global final OS analysis. At this point the database will be closed and any SAEs will be reported outside of the database.

Objectives

Primary Objective:	**Outcome Measures:**
To assess the efficacy of single agent AZD9291 compared with SoC EGFR-TKI therapy as measured by progression free survival (PFS).	- PFS according to RECIST v1.1 by Investigator assessment.

Secondary Objectives:	**Outcome Measures:**
To assess the efficacy of AZD9291 compared with SoC EGFR-TKI therapy by assessment of PFS in patients with: - Positive (or negative) pre-treatment T790M (amino acid substitution at position 790 in EGFR, from a threonine to a methionine) mutation. - EGFR Ex19del or L858R mutation. - EGFRm+ Ex19del or L858R detectable in plasma-derived circulating tumour deoxyribonucleic acid (ctDNA)	- PFS according to RECIST v1.1 by Investigator assessment.
To further assess the efficacy of AZD9291 compared with SoC EGFR-TKI therapy.	- Objective Response Rate (ORR) - Duration of Response (DoR) - Disease Control Rate (DCR) - Depth of response All according to RECIST v1.1 using Investigators assessments.
To further assess the efficacy of AZD9291 compared with SoC EGFR-TKI therapy	Overall survival (OS)
To characterise the pharmacokinetics (PK) of AZD9291 and its metabolites (AZ5104 and AZ7550).	Plasma concentrations of AZD9291 and metabolites AZ5104 and AZ7550; and ratio of metabolite to AZD9291 at predose and 0.5 to 2 hours and 3 to 5 hours postdose.
To assess the impact of AZD9291 compared to SoC EGFR-TKI therapy on patients' disease-related symptoms and Health Related Quality of Life (HRQoL).	- Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30): - Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13).
To assess patient satisfaction with treatment when receiving AZD9291 compared with SoC EGFR-TKI therapy	Cancer Therapy Satisfaction Questionnaire 16 items (CTSQ-16).

Safety Objective:	**Outcome Measure:**
To assess the safety and tolerability profile of AZD9291 compared with SoC EGFR-TKI therapy	- Adverse events (AEs, graded by Common Terminology Criteria for Adverse Event [CTCAE] version 4.0). - Clinical chemistry, haematology, and urinalysis. - Vital signs, physical examination, body weight. - Digital electrocardiogram (ECG). - Left Ventricular Ejection Fraction (LVEF). - World Health Organization (WHO) Performance Status. - Ophthalmologic assessment.

Exploratory Objectives:	**Outcome Measures:**
CCI	CCI
CCI	CCI
CCI	- CCI. - CCI.
CCI	- CCI - CCI
CCI	CCI

CCI	CCI
CCI	- CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

All primary, secondary and safety objectives are applicable to the patients recruited in China (recruited prior to the end of global recruitment and the additional Chinese patients).

Target patient population

Male and female patients aged 18 years and over (patients from Japan aged at least 20 years) with locally advanced or metastatic pathologically confirmed adenocarcinoma of the lung, not amenable to curative surgery or radiotherapy, with tumour that harbours one of the most common EGFR mutations known to be associated with EGFR-TKI sensitivity (exon 19 deletion; L858R) either alone or in combination with other EGFR mutations as confirmed by a local or a central test. EGFR mutation status should have been determined at local laboratories that are Clinical Laboratory Improvement Amendments (CLIA) certified laboratories in the USA; in other countries, the EGFR mutation status should have been determined locally in an accredited laboratory using a well-validated and robust methodology per expectations of the relevant regulatory authority. Patients must be treatment-naïve for advanced disease and eligible to receive first-line treatment with the selected comparator EGFR-TKI in accordance with local prescribing information.

Duration of treatment

Sites will be required to pre-select the comparator (EGFR-TKI, i.e., gefitinib or erlotinib) to be used prior to the site initiation. A cycle of treatment is defined as 21 days of once daily treatment with AZD9291, gefitinib or erlotinib. Treatment with AZD9291 (80 mg once daily), gefitinib (250 mg once daily), or erlotinib (150 mg once daily) will commence following randomisation.

Patients may continue to receive AZD9291 or gefitinib/erlotinib as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria.

Following objective disease progression according to RECIST 1.1, as per investigator assessment, patients who were randomized to SoC arm may have the option to receive open-label AZD9291 provided the specific criteria are met. For further details on post-progression cross-over to AZD9291 please refer to Section 4.3.5.

Investigational product, dosage and mode of administration

AZD9291 is an oral, potent, selective, irreversible inhibitor of both EGFR-TKI sensitising and resistance mutations in NSCLC with a significant selectivity margin over wild-type EGFR. AZD9291 (80 mg orally, once daily) or matching placebo, in accordance with the randomisation schedule, will be administered. A cycle of treatment is defined as 21 days of once daily AZD9291 treatment.

Comparator product, dosage and mode of administration

A standard of care EGFR-TKI with either gefitinib (250 mg orally, once daily) or erlotinib (150 mg orally, once daily) or corresponding matching placebo, as determined by the randomisation schedule, will be administered. A cycle of treatment is defined as 21 days of once daily EGFR-TKI treatment.

Post-progression Open-Label AZD9291 for patients randomised to gefitnib or erlotinib

Patients who are eligible and choose to cross-over to AZD9291 treatment will be dispensed bottles of AZD9291 80 mg, once daily tablets. For further details on AZD9291 please refer to Section 7.1.

Statistical methods

Approximately, 530 patients will be randomised, globally, in a 1:1 ratio (AZD9291: SoC EGFR-TKI) to this study. The primary endpoint of the study is PFS. The primary analysis of PFS will occur when approximately 359 progression events have been observed out of the globally randomised patients. Once 530 patients have been recruited globally, recruitment will continue in mainland China only until approximately 120 patients have been recruited in China. The China cohort will support standalone safety and efficacy analyses of patients from China (for further details please refer to Section 8.7).

If the true PFS hazard ratio for the comparison of AZD9291 versus SoC EGFR-TKI is 0.71, 359 progression events will provide 90% power to demonstrate a statistically significant difference in PFS at a 5% 2-sided significance level (translating to an approximate improvement in median PFS from 10 to 14.1 months assuming exponential data distribution and proportional hazards).

The analysis of OS will be conducted at approximately 60% maturity when approximately 318 death events (across both arms) have occurred. The analysis of OS in the China cohort will be conducted at approximately 60% maturity when approximately 82 death events (across both arms) have occurred in the China cohort. Alpha will be shared across 2 OS analyses, i.e., at the time of the primary PFS analysis and at the final OS analysis with the overall Type 1 error strongly controlled at 5% (two sided) for the testing of OS. This final OS analysis will be summarised in an addendum to the CSR.

Progression free survival will be analysed using a log rank test stratified by race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). The primary analysis will be based on Investigator-recorded assessment of disease progression by RECIST. A sensitivity analysis of PFS will be performed based on data assessed by a Blinded Independent Central Review (BICR) for all patients.

The 2 secondary endpoints of OS in the overall population and PFS in patients with positive pre-treatment T790M status will be tested after the primary PFS analysis in a hierarchical procedure at the time of the PFS analysis.

An Independent Data Monitoring Committee (IDMC) will be convened, and will meet initially when approximately 100 patients have been randomised and followed up for 3 months (estimated to be 6 months from first patient randomised). Thereafter, the IDMC will conduct further reviews of safety data, for example: when global recruitment ends (estimated to be approximately 15 months from first patient randomised). Further meetings for review of

safety data and supportive efficacy data from all patients may be convened at the discretion of the IDMC to evaluate whether the trial should be stopped due to potential harm to patients.

The IDMC will review safety and supportive efficacy assessments and make recommendations to continue, amend, or stop the study based on findings. Serious adverse events, adverse events, and other safety data will be reviewed, and individual and aggregated safety data will be evaluated by the IDMC. Note no alpha adjustment is required for the IDMC data assessment as the stopping boundary would allow for ruling out harm only. Full details of the number of progression events, number of patients and boundary hazard ratio to determine stopping for harm will be documented in the IDMC Charter prior to the first IDMC safety review meeting. The boundary will not be considered binding and will be used in addition to the accumulating available safety data to decide whether to continue the trial as planned, stop or modify the trial.

The safety and efficacy data collected for the China cohort will be combined with data from the China patients recruited prior to the end of global recruitment, and summarised, analysed and reported in a separate Clinical Study Report. These analyses will be performed when the PFS data from the China patients is of similar maturity to when the analysis of PFS for the globally recruited patients will be conducted; i.e. approximately 68% maturity or 82 PFS events out of the approximately 120 China patients. The primary statistical analysis of the efficacy of AZD9291 for China-only FAS patients will be an assessment of progression free survival based on investigator assessment. Safety and tolerability will be summarised for the China-only Safety Analysis Set.

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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
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
AZ DES	AstraZeneca Data Entry Site
BCRP	Breast Cancer Resistance Protein
BICR	Blinded Independent Central Review
BP	Blood pressure
BRAF	v-Raf murine sarcoma viral oncogene homolog B1
CI	Confidence interval
CK	Creatine kinase
CLIA	Clinical Laboratory Improvement Amendments
cMET	Proto-oncogene encoding Hepatocyte Growth Factor Receptor
CR	Complete response
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Event
*ct*DNA	Circulating tumour deoxyribonucleic acid
CTSQ-16	Cancer Therapy Satisfaction Questionnaire - 16 items
CYP	Cytochrome P450
DCR	Disease Control Rate
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid

Abbreviation or special term	Explanation
DoR	Duration of Response
DUS	Drug Under Study
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic case report form
EDR	Early Discrepancy Rate
EDoR	Expected Duration of Response
EGFR	Epidermal Growth Factor Receptor
EGFRm+	Epidermal Growth Factor Receptor mutation positive
EGFR-TKI	Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items
ePRO	Electronic Patient Reported Outcome
ET	Expectations of Therapy
EU	European Union
EURTAC	EURopean TArceva versus Chemotherapy
Ex19del	Deletions in exon 19
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin Fixed and Paraffin Embedded
FPI	First patient in
FSE	Feelings of Side effects
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GMP	Good Manufacturing Practice
HDPE	High-Density-Polyethylene
HER2	Human Epidermal Growth Factor Receptor 2

Abbreviation or special term	Explanation
HR	Hazard ratio
HRCT	High-resolution computed tomography
HIV	Human immunodeficiency virus
HRQoL	Health Related Quality of Life
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
ILD	Interstitial lung disease
INR	International Normalized Ratio
IP	Investigational Product
IPASS	IRESSA Pan-Asia Study
IRB	Independent Review Board
IUS	Intra uterine System
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
L858R	An amino acid substitution at position 858 in EGFR, from a leucine to an arginine
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDR	Late discrepancy rate
LH	Luteinizing hormone
LIMS	Laboratory Information Management System
LPLV	Last patient last visit
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal-epidermal transition
MHLW	Ministry of Health, Labour and Welfare

Abbreviation or special term	Explanation
MRI	Magnetic resonance imaging
MUGA	Multi Gated Acquisition Scan
NCA	Non-compartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small Cell Lung Cancer
NTL	Non-target lesion
OAE	Other significant adverse events
ORR	Objective Response Rate
OS	Overall Survival
P13K	Phosphatidylinositide 3-kinases
PART	Post Analysis and Reporting Team
PAS	Pharmacokinetic Analysis Set
PD	Progression of disease
PFS	Progression free survival
PFS2	Time from randomization to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetics
PR	Partial response
PRO	Patient Reported Outcome
PRO-CTCAE	Patient Reported Outcome version of the Common Terminology Criteria for Adverse Event System approximately 17 items
QCP	Quantitative Clinical Pharmacology
QT	Interval on the electrocardiogram representing the duration of depolarization and repolarization of the heart
QTc	The QT interval corrected for heart rate
RAC	Accumulation ratio
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RET	Ret proto-oncogene
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Abbreviation or special term	Explanation
SAS	Safety Analysis Set
SD	Stable disease
SoC	Standard of Care
SPC	Summary of Product Characteristics
SWT	Satisfaction with Therapy
T790M	An amino acid substitution at position 790 in EGFR, from a threonine to a methionine
T790M+	T790M mutation positive
TCS DES	Tata Consultancy Services Data Entry Site
TFST	Time to first subsequent therapy
TSST	Time to Second Subsequent Therapy
TKI	Tyrosine kinase inhibitor
TL	Target lesion
TSST	Time to second subsequent therapy or death
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
VAS	Visual analog scale
WBDC	Web based data capture
WHO	World Health Organization

1. INTRODUCTION

Lung cancer has been the most common cancer in the world for several decades, and by 2012, there were an estimated 1.8 million new cases, representing 12.9% of all new cancers. It was also the most common cause of death from cancer, with 1.59 million deaths (19.4% of the total) (GLOBOCAN 2012). Non-small Cell Lung Cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of NSCLC patients already have locally advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of early stage NSCLC patients who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters & Le Chevalier 2005). Patients presenting with unselected advanced NSCLC have a median overall survival (OS) of 10 to 12 months (Bonomi 2010).

During the past decade, understanding the critical role of the Epidermal Growth Factor Receptor (EGFR) pathway and development of EGFR targeted tyrosine kinase inhibitors (TKI) have led to significant therapeutic advances in NSCLC. Impressive anti-tumor activity was observed in a subset of patients, initially distinguished by their clinical, epidemiologic and histologic characteristics, and subsequently defined by the presence of activating mutations of EGFR (Lynch et al 2004). The benefit of these TKIs in patients with EGFR mutations (EGFRm+) was initially demonstrated in the second-line and maintenance settings and subsequently confirmed in the first-line setting. Such activating mutations are seen in 10 to 15% of NSCLC patients in the Western world and 30 to 40% in Asia. As a result of first-line studies comparing a TKI versus chemotherapy in EGFRm+ patients (IRESSA Pan-Asia Study [IPASS] and EURopean TArceva versus Chemotherapy [EURTAC]), the National Comprehensive Cancer Network (NCCN) and European Medicines Agency (EMA) currently recommend treatment with an EGFR TKI (erlotinib, gefitinib, or afatinib) in the front-line setting for those patients with documented activating EGFRm+.

In patients with sensitizing mutations of EGFR, response rates of 50 to 80% have been reported with first-line TKI treatment, compared with less than 30% with conventional chemotherapy. Unfortunately, patients ultimately develop acquired resistance to these agents with progression of disease after approximately 9 to13 months.

Currently, there are thoughts to be 2 predominant mechanisms for acquired resistance: a secondary amino acid substitution at position 790 in EGFR, from a threonine to a methionine (T790M) “gatekeeper mutation” of EGFR that renders first-line TKI agents ineffective, and mesenchymal-epidermal transition (MET) amplification that activates phosphatidylinositide 3-kinases (PI3K) signaling independent of EGFR. While other mechanisms of resistance exist, such as oncogenic mutations in the PI3K subunits that allow for EGFR-independent cell survival and small cell transformation, the EGFR T790M secondary mutation accounts for approximately 50 to 60% of cases of acquired resistance to gefitinib or erlotinib.

Initial data showed that T790M mutation occurs in less than 3% of the EGFRm+ patients before starting EGFR-TKI therapy (Pao et al 2005). More recently, using high sensitivity

methods, the EGFR T790M mutation was detected in up to 40% of previously untreated NSCLC, suggesting that presence of de novo resistant clones may be more common than previously appreciated (Arcila et al 2011).

Regardless of whether these resistant clones are in fact acquired or existed de novo, there is an unmet need for therapies which may prevent or delay their clinical emergence, thereby prolonging the time to development of resistance.

1.1 Background and rationale for conducting this study

Activation of the EGFR tyrosine kinase triggers a cascade of intracellular downstream signalling events affecting cell proliferation, survival, angiogenesis and, potentially, metastases. Selective inhibition of EGFR tyrosine kinase has demonstrated clinical benefit in approximately 70% of patients with advanced NSCLC harbouring the EGFR sensitising mutations (the most common of which are exon 21 (L858R) substitution and deletions in exon 19 [Ex19del], described collectively as EGFR mutation). The tumours initially respond to EGFR-TKIs, but subsequently develop resistance to therapy, with a median time to progression of nine months. Besides testing for the presence of EGFR L858R, Ex19del, and T790M mutations in the tumour tissue biopsies, a sequencing method has been developed to detect sensitising EGFR mutations and the emergence of the T790M resistance mutation in circulating tumour deoxyribonucleic acid (ctDNA). Studies show that this novel method using plasma may allow for earlier identification of resistance in patients treated with targeted therapy without the need for invasive biopsies (Goldberg et al 2014).

AZD9291 is a potent irreversible inhibitor of both the single mutant EGFRm+ (TKI sensitivity conferring mutation) and double mutant EGFRm+/T790M+ (TKI resistance conferring mutation) receptor forms of EGFR with a significant selectivity margin over wild-type EGFR. As a result, AZD9291 can effectively block EGFR signalling both in EGFR single mutant cells with activating EGFR mutations and in double mutant cells bearing both the primary EGFR activating and secondary resistance T790M mutation. It is also anticipated that achieving separation in activity between EGFR wild type and activating/T790M (resistance) mutations will provide distinct advantages over less selective first generation EGFR-TKIs with respect to toxicities from EGFR wild type inhibition (skin rash and diarrhoea). Indeed, preliminary data from an ongoing phase I study (D5160C00001) in EGFRm+/T790M+ NSCLC, including treatment naïve patients (i.e., first-line) in addition to relapsed refractory patients, has demonstrated good evidence of efficacy while treatment with AZD9291 has been well tolerated across a range of doses (Ranson et al 2013, Janne et al 2014).

Pre-clinical data provides good evidence to support AZD9291 as a potentially better treatment option for first-line advanced EGFRm+ NSCLC compared to currently approved EGFR TKIs. Unlike gefitinib, erlotinib, and afatinib, emergence of T790M does not appear to be a mechanism of resistance to AZD9291 preclinically (Cross et al 2014), and in vitro data supports a slower time to resistance in response to AZD9291 treatment than that of first and second generation EGFR TKIs. In a pre-clinical mouse model of EGFRm+ NSCLC, AZD9291 achieved superior durable complete responses compared to those achieved with

gefitinib (Cross et al 2014). Furthermore, emerging preclinical data indicate that AZD9291 may have the potential to target brain metastases (a common site of relapse in NSCLC) more effectively than current EGFR TKIs (Kim et al 2014). These data suggest that AZD9291 could offer prolonged PFS over current EGFR TKIs in the first line setting.

1.2 Rationale for study design, doses, and control groups

No approved therapies currently exist to specifically target T790M+ acquired EGFR-TKI resistance, which represents the most common resistance mechanism in NSCLC patients with acquired EGFR-TKI resistance. In view of the above, it is hypothesised that AZD9291 has the potential to deliver prolonged clinical benefit versus first-generation EGFR-TKIs in the first-line setting by preventing the most common type of EGFR-TKI resistance. By preventing this escape mechanism, AZD9291 may prolong the duration of tumour response by slowing down the tumour re-growth rate and improving progression-free survival (PFS). The purpose of this study is to evaluate the efficacy and safety of AZD9291 in EGFRm+ NSCLC patients as first-line treatment for advanced disease. Patients randomised to the control arm can receive either erlotinib or gefitinib. These first-generation EGFR-TKIs are commonly used and represent standard of care (SoC) in participating sites in this study. Participating sites will elect to use either erlotinib or gefitinib, the chosen comparator in this study. Doses and administration of the selected EGFR-TKI will be according to the product prescribing guidelines (i.e., gefitinib 250 mg orally once daily and erlotinib 150 mg orally once daily).

The AZD9291 80 mg once daily dose was selected from a review of all available safety, tolerability, pharmacokinetics (PK), and efficacy data from study D5160C00001, in patients with advanced NSCLC. This included patients who have progressed following prior therapy with an EGFR-TKI and EGFRm+ patients who received AZD9291 as first-line treatment for advanced/metastatic NSCLC.

As of April 2014, AZD9291 had been administered as a capsule formulation across the 20 to 240 mg once daily dose range in more than [redacted] with advanced NSCLC who have progressed following prior therapy with an EGFR-TKI: 20 mg (n=21), 40 mg (n=57), 80 mg (n=74), 160 mg (n=60), and 240 mg (n=20). No dose-limiting toxicities (DLTs) have been reported at any dose level in the escalation cohorts during the 21-day DLT evaluation period. Emerging efficacy data have demonstrated durable objective responses from the starting dose level of 20 mg once daily (Porta et al 2011, Ranson et al 2013). The Objective Response Rate (ORR) in relapsed/refractory T790M+ patients was 64% (Janne et al 2014). The Phase II dose for the T790M+ clinical programme has been selected as 80 mg once daily based on both the activity in patients with T790M+ NSCLC and the low incidence of toxicity (Janne et al 2014). The selected 80 mg dose is 4 fold higher than the minimum efficacious dose tested in study D5160C00001, whilst still being one third of the maximum dose level investigated (240 mg).

The dose assessment for the first-line EGFRm programme has incorporated all data from the T790M+ setting, together with an assessment of emerging preliminary data from more than 50 EGFRm+ patients who are receiving AZD9291 as first-line treatment for advanced /metastatic NSCLC ([redacted] at 80 mg and [redacted] at 160 mg). An in-depth review of

the first-line data included evaluation of safety, efficacy, and PK/exposure data and revealed a very consistent picture with the later-line T790M+ data.

Therefore, based on this comprehensive review of all available safety, tolerability, efficacy, and PK data from study D5160C00001, supported by a very robust package of data in approximately 300 first- and later-line patients (with duration of treatment exceeding 10 months for many patients), 80 mg once daily was selected as the recommended dose for the first-line EGFRm clinical programme. This dose is considered to provide the optimum risk /benefit ratio in this patient population and will therefore be used in the FLAURA Phase III study.

Once CCI have been recruited globally, recruitment will continue in mainland China only until approximately CCI have been recruited in China. This is being done to ensure adequate Chinese patient participation to satisfy China FDA requirements. Due to the lengthy timelines for the approval process in China it is anticipated that will not be met before the global recruitment target of CCI is achieved.

The primary endpoint of this study is PFS. This is an appropriate primary efficacy endpoint in this NSCLC population, and it may be associated with an improvement in OS, symptom control, and Health Related Quality of Life (HRQoL) (Janne et al 2014).

Brain metastases are detected in 20 to 30% of patients with advanced NSCLC upon initial diagnosis, and are associated with a poor prognosis (Porta et al 2011). Up to 50% of lung cancer patients will develop brain metastases at some point during the course of their disease. The first generation EGFR-TKI agents have demonstrated only limited efficacy in treating brain metastases (Bai & Han 2013, Shimato et al 2006); however, preclinical data suggest that AZD9291 may be capable of crossing the blood brain barrier (See Investigator Brochure) and potentially may offer better exposure in this anatomically protected location. The central nervous system (CNS) is a common site of first progression for patients receiving treatment with a standard TKI, despite concomitant systemic disease control. Use of a drug which may more effectively penetrate the CNS has the potential to control and prevent or delay the growth of subclinical brain metastases that were below the limits of detection at the time of diagnosis.

Overall, the totality of primary, secondary, and exploratory endpoints in this study will allow a robust characterisation of overall benefit/risk of AZD9291 in the EGFRm+ advanced NSCLC patient population.

1.3 Benefit/risk and ethical assessment

Although there can be no certainty of clinical benefit to patients, the biological hypothesis, non-clinical and, in particular, the preliminary clinical efficacy and safety data with AZD9291 in the ongoing phase I trial (D5160C00001) support the notion that dual EGFR mutation inhibition may be a valid strategy for the treatment of NSCLC tumours driven via this pathway. Specifically the safety profile of AZD9291 in the ongoing phase I trial is favourable

with the majority of toxicities were mild EGFR related adverse events (Common Terminology Criteria for Adverse Event [CTCAE] Grade 1 or 2), i.e. diarrhoea and skin rash. All trials of AZD9291 exclude patients with clinically significant toxicities related to prior treatments in addition to specifically excluding patients with a history of interstitial lung disease (ILD) or clinically active ILD as this is an uncommon but well documented EGFR-related toxicity. Pre-clinical data showed corneal impairment, related to administration of AZD9291, in animals. All patients will be assessed for possible known EGFR-related toxicities and detailed information on the management of EGFR-related gastrointestinal, dermatological, and ophthalmologic toxicities is being provided for all AZD9291 studies.

It is therefore, reasonable and appropriate to evaluate the oral administration of AZD9291 in comparison to a first-generation EGFR-TKI as first-line therapy in delaying the development of EGFR-TKI resistance in EGFRm+ NSCLC patients, according to the proposed study design.

1.4 Study design

This is a Phase III, double-blind, randomised study to assess the efficacy and safety of AZD9291 (80 mg orally, once daily) versus SoC, EGFR-TKI (either gefitinib [250 mg orally, once daily] or erlotinib [150 mg orally, once daily]), as first-line treatment in patients with locally or centrally confirmed EGFRm+, locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy.

Patients will be enrolled based on either a locally available EGFR mutation result, which has been performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified (USA sites) or an accredited laboratory (outside of the USA) or by testing performed at a designated central laboratory. All patients who are enrolled based on locally available EGFR mutation results or who are tested centrally for enrolment, will be required to provide biopsy tissue for central testing of the two most common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del and L858R substitution mutation). This is to allow a sensitivity analysis to be performed for the various local testing methods used to recruit patients to the study by comparing local testing results with the central laboratory. The EGFR mutation status of the patient's tumour will be determined by the designated central laboratory using the cobas® EGFR Mutation Test (Roche).

Patients should continue with their randomised treatment until Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) defined progression or until a treatment discontinuation criterion is met. There is no maximum duration of treatment as patients may continue to receive their randomised treatment beyond RECIST v1.1 defined progression as long as they are continuing to show clinical benefit, as judged by the Investigator. Patients will be followed for progression and survival (See Figure 1 and Table 1).

The primary endpoint for this study is PFS (defined by RECIST v1.1), as assessed by the Investigator. Progression free survival has been chosen as a clinically meaningful outcome measure, representing a direct benefit to the patient that is largely unaffected by the effects of subsequent therapy. The sponsor will be assessing OS as a key secondary endpoint

recognizing that OS is an important objective assessment of clinical benefit, however in this treatment naive population, OS will likely be confounded by the use of subsequent therapies.

The agreement between the treatment effect assessed by the Investigators and the blinded independent central review will be assessed by all patients' scans having a Blinded Independent Central Review (BICR).

Following the primary PFS analysis (patients from global cohort and patients from China cohort) no further RECIST data will be collected. The sites will continue to perform tumour assessments according to their local practice but this information will not be collected in the eCRF and patients wishing to cross-over do not need BICR confirmation.

Up to primary PFS analysis following objective disease progression according to RECIST 1.1, as per investigator assessment, patients who were randomized to SoC arm may have the option to receive open-label AZD9291 provided the following criteria are met, and should the patient wish to do-so:

- Disease progression confirmed by independent central imaging review which must be established prior to a patient being unblinded. (Note: if central confirmation of progression is not confirmed, the patient is not eligible to receive open-label AZD9291 at that time. Should it be in the patients best interests, they may continue to receive randomized treatment and submit the next scan for central imaging review according to the schedule.)

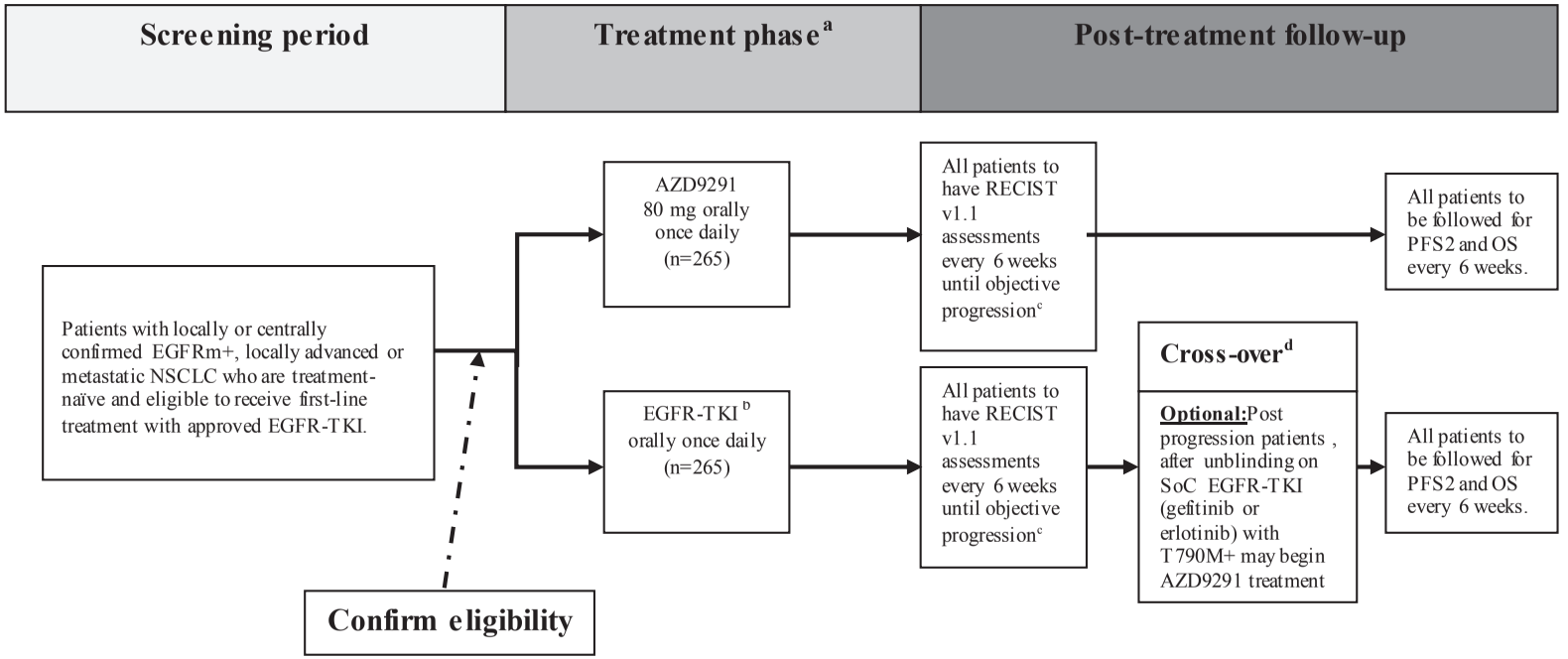
- the patient cannot cross-over if they have received intervening therapy following discontinuation of randomized treatment

- tumour confirmed as T790M mutation positive following disease progression (may be determined before or after a patient has been unblinded.)

Provided the above criteria have been met, and the patient was randomized to the SoC treatment arm, the patient may commence open-label AZD9291. If the patient has been unblinded and they are not eligible for crossover or choose not to crossover, they cannot recommence or continue on their randomized treatment. After IEC/IRB approval of Clinical Study Protocol version 4.0, all patients determined to have objective disease progression as per Investigator's assessment, will be given the opportunity to begin treatment with open-label AZD9291, if eligible; central confirmation of disease progression will no longer be required. Further details on post-progression cross-over to AZD9291 please refer to Section 4.3.5.

On discontinuation of randomised study drug, patients will be treated in accordance with the regional SoC.

Figure 1 Study flow chart prior to primary PFS analysis



EGFRm+ = Epidermal Growth Factor Receptor Mutation Positive; EGFR-TKI = Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor; Ex19del = exon 19 deletion; L858R = exon 21; NSCLC = Non-small Cell Lung Cancer; OS = overall survival; PFS2 = second progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SoC = standard of care.

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 Either gefitinib (250 mg orally, once daily)or erlotinib (150 mg orally, once daily).
c Patients who discontinue treatment prior to disease progression will continue to have RECIST v1.1 assessment every 6 weeks for the first 18 months and then every 12 weeks relative to randomisation until progression. Patients who continue treatment after objective progression due to clinical benefit will be followed up as per standard practice post progression.
d. Patients with objective radiological progression according to RECIST 1.1 by the Investigator and confirmed by independent central imaging review who are on SoC EGFR-TKI (gefitinib or erlotinib) after being unblinded and have T790M mutation test result positive will be given the opportunity to cross-over and begin treatment with AZD9291 80mg, once daily. After data cut-off date for the primary PFS analysis, all patients (except those enrolled in China) determined to have objective disease progression according to RECIST 1.1 as per Investigator's assessment will be given the opportunity to begin treatment with open-label AZD9291, if eligible; central confirmation of disease progression will no longer be required. The patients enrolled in China will be given the opportunity to begin open–label treatment with AZD9291 (if eligible) after the primary PFS analysis for the China patient subgroup.

2. STUDY OBJECTIVES

2.1 Primary objectives

Primary Objective:	Outcome Measures:
To assess the efficacy of single agent AZD9291 compared with SoC EGFR-TKI therapy as measured by PFS.	- PFS according to RECIST v1.1 by Investigator assessment.

2.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
To assess the efficacy of AZD9291 compared with SoC EGFR-TKI therapy by assessment of PFS in patients with: - Positive (or negative) pre-treatment T790M (amino acid substitution at position 790 in EGFR, from a threonine to a methionine) mutation. - EGFR Ex19del or L858R mutation. - EGFRm+ (Ex19del or L858R) detectable in plasma-derived ctDNA.	- PFS according to RECIST v1.1 by Investigator assessment.
To further assess the efficacy of AZD9291 compared with SoC EGFR-TKI therapy	- ORR - Duration of Response (DoR) - Disease Control Rate (DCR) - Depth of response All according to RECIST v1.1 using Investigators assessments.
To further assess the efficacy of AZD9291 compared with SoC EGFR-TKI therapy.	Overall survival (OS)
To characterise the PK of AZD9291 and its metabolites (AZ5104 and AZ7550).	Plasma concentrations of AZD9291 and metabolites AZ5104 and AZ7550; and ratio of metabolite to AZD9291at predose and 0.5 to 2 hours and 3 to 5 hours postdose.

To assess the impact of AZD9291 compared to SoC EGFR-TKI therapy on patients' disease-related symptoms and HRQoL	- Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30): - Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13).
To assess patient satisfaction with treatment when receiving AZD9291 compared with SoC EGFR-TKI therapy	Cancer Therapy Satisfaction Questionnaire 16 items (CTSQ-16)

2.3 Safety objectives

Safety Objective:	**Outcome Measure:**
To assess the safety and tolerability profile of AZD9291 compared with SoC EGFR-TKI therapy.	- Adverse events (AEs, graded by CTCAE version 4.0). - Clinical chemistry, haematology, and urinalysis. - Vital signs, physical examination, body weight. - Digital electrocardiogram (ECG). - Left Ventricular Ejection Fraction (LVEF). - World Health Organization (WHO) Performance Status. - Ophthalmologic assessment.

2.4 Exploratory objectives

Exploratory Objectives:	**Outcome Measures:**
CCI	CCI
CCI	CCI

CCI	- CCI
CCI	- CCI
CCI	CCI
CCI	CCI
CCI	- CCI
CCI	CCI

All primary, secondary and safety objectives are applicable to the patients recruited in China (recruited prior to the end of global recruitment and the additional Chinese patients).

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL

Each patient 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 inclusion in the study, patients must fulfil all of the following criteria:

1. Provision of informed consent prior to any study specific procedures, sampling, and analyses.
2. Male or female, aged at least 18 years. Patients from Japan aged at least 20 years.
3. Pathologically confirmed adenocarcinoma of the lung (e.g., this may occur as systemic recurrence after prior surgery for early stage disease or patients may be newly diagnosed with Stage IIIB/IV disease). Patients with mixed histology are eligible if adenocarcinoma is the predominant histology.
4. Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy.
5. The tumour harbours one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations, assessed by a CLIA-certified (USA sites) or an accredited (outside of the USA) local laboratory or by central testing.
6. Mandatory provision of an unstained, archived tumour tissue sample in a quantity sufficient to allow for central analysis of EGFR mutation status. Please refer to the Laboratory Manual for details.

7. Patients must be treatment- naïve for locally advanced or metastatic NSCLC and eligible to receive first-line treatment with gefitinib or erlotinib as selected by the participating centre. Prior adjuvant and neo-adjuvant therapy is permitted (chemotherapy, radiotherapy, investigational agents) provided all other entry criteria are satisfied
8. World Health Organization Performance Status of 0 to 1 with no clinically significant deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks.
9. 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 computerised tomography (CT) or magnetic resonance imaging (MRI), and which is suitable for accurate repeated measurements. If only one measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.
10. Female patients should be using adequate contraceptive measures, should not be breast feeding, and must have a negative pregnancy test prior to first dose of study drug; or female patients must have an evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

    - Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments.
    - Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the post-menopausal range for the institution.
    - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but not tubal ligation.

11. Male patients should be willing to use barrier contraception, i.e. Condoms
12. For inclusion in the optional genetics research study, patients must provide informed consent for genetic research.

    If a patient declines to participate in any voluntary exploratory research and/or genetic component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

3.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
2. Treatment with any of the following:

- Prior treatment with any systemic anti-cancer therapy for locally advanced/metastatic NSCLC including chemotherapy, biologic therapy, immunotherapy, or any investigational drug.
- Prior treatment with an EGFR-TKI.
- Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study drug.
- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.
- Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of study drug) medications or herbal supplements known to be potent inducers of cytochrome P450 (CYP) 3A4 (Appendix B).
- Alternative anti-cancer treatment.
- Treatment with an investigational drug within five half-lives of the compound or any of its related material, if known.

3. Any concurrent and/or other active malignancy that has required treatment within 2 years of first dose of study drug.
4. Any unresolved toxicities from prior systemic therapy (e.g., adjuvant chemotherapy) greater than CTCAE grade 1 at the time of starting study drug with the exception of alopecia and grade 2, prior chemotherapy-induced neuropathy.
5. Spinal cord compression, symptomatic and unstable brain metastases, except for those patients who have completed definitive therapy, are not on steroids, have a stable neurologic status for at least 2 weeks after completion of the definitive therapy and steroids.
6. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol; or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Active infection will include any patients receiving intravenous treatment for infection; active hepatitis B infection will, at a minimum, include all patients who are Hepatitis B surface antigen positive (HbsAg positive) based on serology assessment. Screening for chronic conditions is not required.
7. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of AZD9291.
8. Any of the following cardiac criteria:

   - Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 ECGs, using the screening clinic ECG machine-derived QTcF value.

- 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, PR interval >250 msec.
- Any patient with any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval.

9. Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.
10. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values.
    - Absolute neutrophil count <1.5 x 10^9/L.
    - Platelet count <100 x 10^9/L.
    - Haemoglobin <90 g/L.
    - Alanine aminotransferase (ALT) >2.5x the upper limit of normal (ULN) if no demonstrable liver metastases or >5xULN in the presence of liver metastases.
    - Aspartate aminotransferase (AST) >2.5xULN if no demonstrable liver metastases or >5xULN in the presence of liver metastases.
    - Total bilirubin >1.5xULN if no liver metastases or >3xULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or liver metastases.
    - Creatinine >1.5xULN concurrent with creatinine clearance <50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5xULN.
11. Women who are breast feeding.
12. History of hypersensitivity to active or inactive excipients of AZD9291 or drugs with a similar chemical structure or class to AZD9291.
13. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.
14. [redacted]

3.3 Patient enrolment and randomisation

Investigators should keep a record in the screening log of patients who entered the screening.

The Investigators will:

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

2. Obtain a unique 7-digit enrolment number (E-code) through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) in the following format ECCNNXXX: CC being the country code, NN being the centre number, and XXX being the patient enrolment code at the centre.

3. Determine patient eligibility. See Section 3.1 and 3.2

   - At Visit 2, once the patient is confirmed to be eligible, the Principal Investigator or suitably trained delegate will:

4. Obtain a unique randomisation number via IVRS/IWRS.

   - If a patient is re-screened, a new E-code will always be assigned.

   - If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

Note: Section 4.1 describes the procedures to be carried out during Screening period.

3.4 Procedures for handling incorrectly enrolled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study drug. There can be no exceptions to this rule.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the Study Physician immediately, and a discussion should occur between the Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The Study Physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Eligible patients will be centrally randomised to receive either AZD9291 80 mg orally once daily or the site pre-selected EGFR-TKI (gefitinib 250 mg orally once daily or erlotinib 150 mg orally once daily) in a 1:1 ratio using the IVRS/IWRS system. The actual EGFR-TKI has to be selected at a site/country level according to country's marketing authorization prior to the site initiation.

Patients will be stratified at randomization based on EGFR mutation (Ex19del or L858R) and race (Asian or Non-Asian).

3.6 Methods for ensuring blinding

Investigational product (IP, also referred to as 'study drug' in this protocol) will be labelled using a unique material pack code, which is linked to the randomisation code. The IVRS/IWRS will assign the bottles of study material to be dispensed to each patient. This is a double-dummy study wherein each patient will receive either the active AZD9291 plus comparator-matching placebo or active comparator plus AZD9291-matching placebo. The active and placebo tablets will be identical and presented in the same packaging to ensure blinding of the medication.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigators or pharmacists from the IVRS/IWRS. Routine procedures for this will be described in the IVRS/IWRS user manual that will be provided to each site.

The treatment code may be broken in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. (e.g. for crossover from SoC to AZD9291). The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

Should there be a requirement to unblind a patient for reasons other than to determine suitability for cross-over to AZD9291, central confirmation of RECIST 1.1 disease progression is not required. See Section 4.3.5 for further details of requirements for the post-progression cross-over to AZD9291.

At the time of unblinding for primary PFS for analysis, patients excluded from the global cohort will remain blinded.

3.8 Restrictions

The following restrictions apply while the patient is receiving study drug (AZD9291, gefitinib, and erlotinib) and for the specified times before and after:

1. Female patients of child-bearing potential should use acceptable methods of contraception from the time of screening until 6 weeks after discontinuing study drug. Acceptable methods are provided in Appendix I.

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. Male patients

should avoid procreation for 4 months after completion of study drug treatment. Patients should refrain from donating sperm from the start of dosing until 4 months after discontinuing study drug treatment.

3. Once enrolled, all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known potent inducers of CYP3A4 whenever feasible; but patients may receive any medication that is clinically indicated for treatment of comorbidities. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of AZD9291. All concomitant medications should be captured on the electronic case report form (eCRF). Guidance on medicines to avoid, medications that require close monitoring, and on washout periods is provided (See Appendix B). The use of medications known to prolong QTc interval should be avoided whenever feasible unless clinically indicated to for treatment of comorbidities. Current information on drugs known to prolong QTc interval can be found on the Arizona Center for Education and Research on Therapeutics website: https://crediblemeds.org/ The website categorises drugs based on the risk of inducing Torsades de Pointes (TdP)

4. If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see above), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon Breast Cancer Resistance Protein (BCRP) 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. Guidance on medications to avoid, medications that require close monitoring, and on washout periods should be provided (See Appendix B).

5. Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosvuastatin must be stopped and any appropriate further management should be taken.

3.9 Discontinuation from investigational product

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue his/her participation in the study, without prejudice.
- Adverse event.
- Pregnancy.
- Severe non-compliance with the study protocol as judged by the Investigator and/or AstraZeneca.
- Patients who are incorrectly initiated on IP.

- Objective disease progression as per RECIST v1.1 or patient is no longer receiving clinical benefit.

Patients experiencing any of the following adverse events will not be permitted to restart study treatment:

- Interstitial Lung Disease (ILD)
- QTc interval prolongation with signs/symptoms of serious arrhythmia as criteria for not restarting study treatment which aligns with updated Investigator Brochure Content
- AEs of CTCAE grade 3 or more that are not attributable to the disease or disease-related processes under investigation, which do not resolve to ≤CTCAE grade 1 after 2 weeks of IP discontinuation.

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP or withdraw from the study (i.e., IP and assessments – See Section 3.10), without prejudice to further treatment. A patient that decides to discontinue IP will always be asked about the reason(s) for discontinuation of IP and the presence of any AEs. If possible, they will be seen and assessed by the Investigator(s). The Investigator will follow up AEs outside of the clinical study (See Section 6.3.2). The patient or representative will return all unused study drugs.

Any patient who discontinues IP treatment for reasons other than objective disease progression should have tumour assessments performed as scheduled in the protocol (See Table 1) until objective disease progression is documented or death occurs, unless consent is withdrawn. (Note: following the primary PFS analysis (among Global cohort and China cohort) tumour assessments will no longer be collected). SAEs must be collected up to the end of the survival follow-up.

Note: Some assessments such as further anti-cancer treatment should continue beyond first objective progression throughout the survival assessment period (See Table 1 and Table 3).

Following objective disease progression according to RECIST 1.1, as per investigator assessment, patients who were randomized to SoC arm may have the option to receive open-label AZD9291 provided the specific criteria are met, and should the patient wish to do-so. For further details on post-progression cross-over to AZD9291 please refer to Section 4.3.5.

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

At any time, patients are free to discontinue IP treatment and withdraw from the study (i.e., study treatment and assessments), without prejudice to further treatment. A patient who decides to discontinue IP treatment and assessments will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up (See Section 6.3.2); ePRO devices and all IPs should be returned by the patient or caretaker. The term withdrawal from the study refers to both the discontinuation from the IP treatment and study assessments.

Reasons for withdrawal from the study:

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

If patients wish to withdraw their consent to both study drug and study assessments, they should be asked if they are willing to continue with survival follow-up (which can be conducted by telephone). If patients wish to withdraw their consent to further participation in the study entirely, including survival follow-up, this should be clearly documented in the patient notes and in the clinical study database.

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

Withdrawn patients will not be replaced.

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Eligibility Criteria not Fulfilled' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (study drug and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. Investigator will follow up AEs outside of the clinical study (See Section 6.3.2). The patient or representative will return the ePRO and all unused study drugs.

Adverse events will be followed up (See Section 6.3.2); electronic questionnaire devices (ePRO) and all unused study drugs should be returned by the patient or representative.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn patients will not be replaced.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, study patients 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.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

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

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study plan (up to Primary PFS Analysis for Global Patients and up to China PFS Analysis for China Cohort)

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles after Cycle 7)								Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+[a]	Treatment Discontinuation (IP and/or study)	28-day follow-up[b]	Progression follow-up	Survival follow-up	
Cycle[c]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-C6 D1	C7+ D1	NA	NA	NA	NA	
Day	-28	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)	NA	0	±2	±2	±2	±7	±7	±7	± 7	± 7	± 7	± 7	SECTION
Informed consent[d]	X												1, 10.4
Tumour material (sufficient quantity) for central confirmation of EGFR mutation status and retrospective T790M testing & additional (optional) material for exploratory analyses	X												5.1.4
Demography & baseline characteristics	X												3

Table 1 Study plan (up to Primary PFS Analysis for Global Patients and up to China PFS Analysis for China Cohort)

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles after Cycle 7)								Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+[a]	Treatment Discontinuation (IP and/or study)	28-day follow-up[b]	Progression follow-up	Survival follow-up	
Cycle[c]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-C6 D1	C7+ D1	NA	NA	NA	NA	
Day	-28	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)	NA	0	±2	±2	±2	±7	±7	±7	± 7	± 7	± 7	± 7	SECTION
Medical/surgical history	X												3
Inclusion/exclusion	X	X											2, 3.2
Physical examination including weight[e]	X	X			X	X	X	X then every 6w	X				5.2.2
Height	X												5.2.2
WHO performance status	X	X			X	X	X	X then every 6w	X		X At start of subsequent treatment		5.3.1

Table 1 Study plan (up to Primary PFS Analysis for Global Patients and up to China PFS Analysis for China Cohort)

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles after Cycle 7)								Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+[a]	Treatment Discontinuation (IP and/or study)	28-day follow-up[b]	Progression follow-up	Survival follow-up	
Cycle[c]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-C6 D1	C7+ D1	NA	NA	NA	NA	
Day	-28	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)	NA	0	±2	±2	±2	±7	±7	±7	± 7	± 7	± 7	± 7	SECTION
Pregnancy test (pre-menopausal female patients only)	X												5.2.1
Ophthalmologic assessment	X	← as clinically indicated →											5.2.7.1
Vital signs[e]	X	X	X	X	X	X	X	X then every 6w	X				5.2.5
Clinical chemistry/ Haematology/ Urinalysis[e]	X	X	X	X	X	X	X	X then every 6w	X				5.2.1

Table 1 Study plan (up to Primary PFS Analysis for Global Patients and up to China PFS Analysis for China Cohort)

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles after Cycle 7)							Treatment Discontinuation (IP and/or study)	Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+[a]		28-day follow-up[b]	Progression follow-up	Survival follow-up	
Cycle[c]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-C6 D1	C7+ D1	NA	NA	NA	NA	
Day	-28	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)	NA	0	±2	±2	±2	±7	±7	±7	± 7	± 7	± 7	± 7	SECTION
Digital ECG[f]	X	X	X	X	X	X	X	X then every 6w	X	X[p]			5.2.3
Echocardiogram/MUGA (for LVEF)	X	every 12 weeks relative to first dose and as clinically required							X				5.2.4
PK blood sample (including metabolites)[g]		X				X	X	X[g] every other cycle					5.4

Table 1 Study plan (up to Primary PFS Analysis for Global Patients and up to China PFS Analysis for China Cohort)

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles after Cycle 7)								Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+[a]	Treatment Discontinuation (IP and/or study)	28-day follow-up[b]	Progression follow-up	Survival follow-up	
Cycle[c]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-C6 D1	C7+ D1	NA	NA	NA	NA	
Day	-28	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)	NA	0	±2	±2	±2	±7	±7	±7	± 7	± 7	± 7	± 7	SECTION
Tumour samples upon disease progression (optional)									X (op)				5.7.2
Plasma sample for ctDNA and blood borne biomarkers	X	X pre-dose	X	X	X	X	X	X then every 6w	X		X[h]		5.7.3
Genetic consent and blood sample (optional)[i]	X												5.6
Tumour assessments (RECIST v1.1)[j]	X	every 6 weeks for the first 18 months and then every 12 weeks relative to randomisation until progression /Per standard practice post-progression											5.1.1

Table 1 Study plan (up to Primary PFS Analysis for Global Patients and up to China PFS Analysis for China Cohort)

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles after Cycle 7)								Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+[a]	Treatment Discontinuation (IP and/or study)	28-day follow-up[b]	Progression follow-up	Survival follow-up	
Cycle[c]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-C6 D1	C7+ D1	NA	NA	NA	NA	
Day	-28	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)	NA	0	±2	±2	±2	±7	±7	±7	± 7	± 7	± 7	± 7	SECTION
EORTC QLQ-C30[k]		X pre-dose	every 6w relative to first dose						X		X at progression and every 6 w	X at progression and every 6 w[l]	5.3.4.1
EORTC QLQ-LC13[k]		X pre-dose	weekly relative to first dose for first 6 weeks of treatment				after first 6 weeks of treatment every 3w relative to first dose		X		X at progression and every 3w	X at progression and every 3w[l]	5.3.4.1

Table 1 Study plan (up to Primary PFS Analysis for Global Patients and up to China PFS Analysis for China Cohort)

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles after Cycle 7)							Treatment Discontinuation (IP and/or study)	Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+[a]		28-day follow-up[b]	Progression follow-up	Survival follow-up	
Cycle[c]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-C6 D1	C7+ D1	NA	NA	NA	NA	
Day	-28	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)	NA	0	±2	±2	±2	±7	±7	±7	± 7	± 7	± 7	± 7	SECTION
PRO CTCAE[k]		X pre-dose	weekly relative to first dose for first 18w of treatment					X then every 3w	X		X at progression and every 3 w	X at progression and every 3 w[l]	5.3.4.3
CTSQ-16[k]					X	X[m]							5.3.4.2
Health Resource Use Module		X pre-dose	every 6 weeks relative to first-dose -						X		X every 6 w and at progression	X every 6 w and at progression [l]	5.3.4.5

Table 1 Study plan (up to Primary PFS Analysis for Global Patients and up to China PFS Analysis for China Cohort)

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles after Cycle 7)								Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+[a]	Treatment Discontinuation (IP and/or study)	28-day follow-up[b]	Progression follow-up	Survival follow-up	
Cycle[c]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-C6 D1	C7+ D1	NA	NA	NA	NA	
Day	-28	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)	NA	0	±2	±2	±2	±7	±7	±7	± 7	± 7	± 7	± 7	SECTION
Dispense study drug		X			X	X	X	X then every 6w					7.2
Dose with study drug		daily dosing											7.2
Concomitant medication											X done if prior to 28-day follow-up		5.3.2
Adverse events											X done if prior to 28-day follow-up		6.3

Table 1 Study plan (up to Primary PFS Analysis for Global Patients and up to China PFS Analysis for China Cohort)

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles after Cycle 7)								Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+[a]	Treatment Discontinuation (IP and/or study)	28-day follow-up[b]	Progression follow-up	Survival follow-up	
Cycle[c]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-C6 D1	C7+ D1	NA	NA	NA	NA	
Day	-28	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)	NA	0	±2	±2	±2	±7	±7	±7	± 7	± 7	± 7	± 7	SECTION
Anti-cancer and surgery treatment	X										X	X	5.3.3
Subsequent response/progression data[n]												X (every 6 weeks)	5.1.3
Survival status[o]												X (every 6w)	4.3.4

C = cycle; ctDNA = circulating tumour deoxyribonucleic acid; CTSQ-16 = Cancer Therapy Satisfaction Questionnaire 16-item; D = day; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; EORTC QLQ-C30; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items; IP = investigational product; LVEF = Left Ventricular Ejection Fraction; MUGA = Multi Gated Acquisition Scan; op = optional; PRO CTCAE = Patient Reported Outcome version of the Common Terminology Criteria for Adverse Event approximately 17 items; PK = pharmacokinetics; RECIST v 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SoC = standard of care; T790M = an amino acid substitution at position 790 in EGFR, from a threonine to a methionine; w = weeks; WHO = World Health Organization.

[a] Patients to attend visits every 6 weeks from Cycle 7 onwards.

[b] As a minimum, telephone contact should be made with the patient 28 days (+ 7 days) following the discontinuation of study drug.

[c] A cycle is defined as a 21-day Treatment period.

[d] Consent may be taken prior to 28-day window if required. Screening period will then start with first study-related assessment.

[e] The assessments are to be completed pre-dose on visit day. If screening assessments have been performed within 14 days prior to starting study treatment, they do not have to be repeated on Visit 2 if the patient's condition has not changed.

[f] All ECG data (with the exception of the screening ECGs) will be collected digitally. Electrocardiogram is also to be performed in event of any cardiac AE.

[g] Plasma PK sampling (2 mL each) will be performed at pre-dose, 0.5 to 2 hours, and 3 to 5 hours post-dose at Day 1 Cycle 1 and every other cycle thereafter up to and including Cycle 13.

[h] If a patient discontinues study treatment prior to progression, samples should continue to be collected every 6 weeks until objective disease progression at time points corresponding to RECIST assessment.

[i] If for any reason the sample is not drawn prior to dosing, it may be taken at any visit until the last study visit.

[j] The baseline assessments should be performed within 28 days prior to study drug initiation. Subsequent assessments are to be performed every 6 weeks (±1 week) relative to randomisation for the first 18 months (78 weeks) and then every 12 weeks (±1 week) until objective disease progression as per RECIST v1.1, even if a patient discontinues treatment prior to progression or receives other anti-cancer treatment.). Tumour assessment will be performed using contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and abdomen (including liver and adrenal glands). Any other sites where disease is suspected or known at baseline must also be imaged. Duplicate images will be collected for independent review. Scans will continue to be submitted up to the point of progression as assessed by the investigator. Please refer to Section RECIST V1.1 for more details.

[k] The questionnaire for ePRO is available for a period for up to 5 days for each assessment (i.e., it will be available two days before the designated "Study Day" and two days after the designated "Study Day") for completion.

[l] PROs to be collected up to second progression (PFS2).

[m] CTSQ-16 will be administered via an electronic device. Day 43 visit (i.e., Cycle 3, Day 1 visit) should be scheduled close to Day 43 (±2 days), so that ePROs can be completed before the scan. Where it is not possible to follow this guidance, the timing of the tumour assessment should be prioritised over the assessment of ePRO.

[n] Investigator assessment of response to be collected.

[o] Patients should be contacted in the week after data cut-off for each study analysis (primary progression free survival [PFS] and overall survival [OS]) to establish survival status.

[p] A 28-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.

Table 2 **Study plan for post-progression cross-over to AZD9291 from SoC treatment arm up to Primary PFS Analysis**

Visit	Pre - Cross-over to AZD9291 Visit	Treatment with AZD9291 Period							AZD9291 Treatment Discontinuation	Survival follow-up	For details see Protocol Section
		2	3	4	5	6	7	10+[a]			
Cycle/ Day	C0	C1	C1	C1	C2	C3	C4-C6	C7	NA	NA	
Day	NA	1	8	15	22	43	64-106	127	NA	NA	
Window (days)	NA	0	+2	+2	+2	+7	+7	+7	+ 7	+ 7	SECTION:
Collect/submit sample for T790M mutation assessment	X[b]										5.7.3
Tumour assessments	X	← as per local practice →									5.1.2
Subsequent response/ progression data[h]		← every 6 weeks relative to randomisation →								X (every 6 weeks)	5.1.3
Physical examination, including weight		X			X	X	X	X then every 6 weeks	X		5.2.2
WHO Performance status		X			X	X	X	X then every 6 weeks	X	X	5.3.1
Ophtalmologic assessments		← As clinically indicated →									5.2.7.1

Table 2 **Study plan for post-progression cross-over to AZD9291 from SoC treatment arm up to Primary PFS Analysis**

Visit	Pre - Cross-over to AZD9291 Visit	Treatment with AZD9291 Period							AZD9291 Treatment Discontinuation	Survival follow-up	For details see Protocol Section
		2	3	4	5	6	7	10+[a]			
Cycle/ Day	C0	C1	C1	C1	C2	C3	C4-C6	C7	NA	NA	
Day	NA	1	8	15	22	43	64-106	127	NA	NA	
Window (days)	NA	0	+2	+2	+2	+7	+7	+7	+ 7	+ 7	SECTION:
Vital signs (pulse and BP)[c]		X	X	X	X	X	X	X then every 6 weeks	X		5.2.5
Clinical chemistry/ Haematology /Urinalysis[c]		X	X	X	X	X	X	X then every 6 weeks	X		5.2.1
Digital ECG		X	X	X	X	X	X	X then every 6 weeks	X		5.2.3
Echocardiogram/MUGA (for LVEF)		X	every 12 weeks relative to Cycle 1 Day 1 of crossover AZD9291 treatment and as clinically required						X		5.2.4
EORTC QLQ-C30[d] (by e-device)	every 6 weeks[e]										5.3.4.1
EORTC QLQ LC13 (by e-device) PRO-CTCAE (by e-device)[d]	every 3 weeks[f]										5.3.4.1 5.3.4.3

Table 2 Study plan for post-progression cross-over to AZD9291 from SoC treatment arm up to Primary PFS Analysis

Visit	Pre - Cross-over to AZD9291 Visit	Treatment with AZD9291 Period							AZD9291 Treatment Discontinuation	Survival follow-up	For details see Protocol Section
		2	3	4	5	6	7	10+[a]			
Cycle/ Day	C0	C1	C1	C1	C2	C3	C4-C6	C7	NA	NA	
Day	NA	1	8	15	22	43	64-106	127	NA	NA	
Window (days)	NA	0	+2	+2	+2	+7	+7	+7	+ 7	+ 7	SECTION:
Dose with AZD9291		Daily ← →									7.2
Concomitant medication & procedures	← →										5.3.2
Adverse events	← →								X		6.
Survival Status										X[g]	4.3.4
Anti-cancer treatment	X								X	X[g]	5.3.3

a. After cycle 7 the cycle is defined as 42-day treatment period
b. the sample that is used to test for the mutation to be eligible to go on to the X-over arm, can be the same as the optional sample at progression.
c. To be completed pre-dose on visit day.
d. The questionnaire for ePRO is available for a period of up to 5 days for each assessment (ie, it will be available two days before the designated "Study Day" and two days after the designated "Study Day") for completion.
e. Assess every 6 weeks (± 1 week) relative to randomization until end of study (including survival follow-up period) and at the time of progression.
f Assess every 3 weeks (± 3 days) relative to randomization until end of study (including survival follow-up period) and at the time of progression.
g. Survival status including anti-cancer treatment to be performed every 6 weeks (relative to randomization) following disease progression or withdrawal from treatment. [Note: Additional survival calls will be made in the 1 week following the date of the data cut-off for each OS analysis.]
h. Investigator assessment of response to be collected.

Table 3 Study Schedule Post Primary PFS Analysis and up to the Final OS Analysis

Visit	Treatment post primary PFS analysis every 84 days (12 weeks)	Treatment Discontinuation (IP and/or study)	Follow-up Period			For details see Protocol Section
			28-day Follow-up[b]	Progression Follow-up	Survival Follow-up	
Cycle[a]/Day	C7+ D1	NA	NA	NA	NA	
Window (days)	±7	NA	±7	±7	±7	
Tumour samples upon disease progression (optional)		X				5.7.2
Physical examination, including weight	X	X				5.2.2
Ophthalmolgic assessment	as clinically indicated					5.2.7.1
Plasma sample for ctDNA and blood borne biomarkers		X[h]		X[h]		5.7.3
Vital signs (pulse and BP)[m]	X	X				5.2.5
Clinical chemistry/ Haematology/Urinalysis[m]	X	X				5.2.1
ECG assessment[e]	X	X	X[c]			5.2.3

Table 3 Study Schedule Post Primary PFS Analysis and up to the Final OS Analysis

Visit	Treatment post primary PFS analysis every 84 days (12 weeks)	Treatment Discontinuation (IP and/or study)	Follow-up Period			For details see Protocol Section
			28-day Follow-up[b]	Progression Follow-up	Survival Follow-up	
Cycle[a]/Day	C7+ D1	NA	NA	NA	NA	
Window (days)	±7	NA	±7	±7	±7	
Echocardiogram/MUGA	X	X				5.2.4
Tumour assessments	As per local clinical practice					5.1.1
Dispense study drug	X					7.2
Dose with study drug	daily dosing					7.2
Concomitant medication & procedures	←	→		X done if prior to 28-day follow-up		7.7
Adverse events[j]	←	→		X done if prior to 28-day follow-up	X[f]	6.3
Survival Status					X[k]	4.3.4
Anti-cancer and surgery treatment				X	X[k]	5.3.3

a A cycle is defined as 21-day treatment period.
b As a minimum, telephone contact should be made with the patient 28 days (+ 7 days) following the discontinuation of study drug as long as no ECG follow up is required
c A 28-day follow-up assessment will be required if on treatment assessment was abnormal at treatment discontinuation.
e Post PFS analysis, ECGs will be collected locally and stored at the site.
f. SAEs collection only, up to the end of the survival follow-up
h. ct DNA samples will be collected at the time of treatment discontinuation and at the time of progression only for patients that have not crossed -over
j. Following treatment discontinuation, SAEs considered related to study procedures should continue to be collected as outlines in Section 6.3
k. Survival status including anti-cancer treatment to be performed every 6 weeks (relative to randomization) following disease progression or withdrawal from treatment. [Note: Additional survival calls will be made in the 1 week following the date of the data cut-off for each OS analysis.]
m. To be completed pre-dose on visit day.

4.1 Enrolment/screening period

It is recommended that the screening assessments be performed in a stepwise process beginning with the confirmation of EGFR mutation status either from mutation testing results available locally where testing has been performed by a CLIA-certified (USA sites) or an accredited (outside of the USA) or determined by the designated central laboratory. However, screening assessments may be done in parallel to the EGFR mutation assessment, as appropriate. Procedures will be performed according to the Study Plan (See Table 1). Tumour assessments and other clinical data obtained as SoC prior to consent may be used for the study, provided the assessments fall within the protocol specified period prior to the first dose of the study drug.

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be randomised into the study.

The following will be performed at screening:

Written informed consent

Each potential patient will provide written informed consent prior to starting any study specific procedures (see Section 10.4).

- All patients will be required to provide consent to supply a tumour biopsy sample taken during the Screening period or a pre-study tumour biopsy sample for entry into this study. Patient will also be required to provide consent for collection of blood samples both during the Screening period and during study treatment. Patients will be required to provide consent for these samples to be used for diagnostic development. This consent is included in the main patient informed consent form (ICF).
- Additionally, patients will be given the option to consent to the [redacted], and the host pharmacogenetics research component of the study, each in a separate ICF.

Assignment of patient screening/randomisation number

As per standard, enrolment number (E-code) is assigned to the patient and Principal Investigator or delegate should perform enrolment/screening call (See Section 3.3). During the randomisation visit (Visit 2), patient will receive randomisation number via IVRS/IWRS.

Demography

- Demographic data and other characteristics will be recorded and will include date of birth or age, gender, race and/or ethnicity, and smoking history.

Medical/surgical history

- A standard medical and surgical history will be obtained.

4.2 Treatment period (up to primary PFS analysis)

A cycle of treatment is defined as 21 days of once daily treatment with AZD9291, gefitinib or erlotinib. Patients will be randomised at Visit 2 and receive either AZD9291 or EGFR-TKI (gefitinib or erlotinib). Patient will continue study treatment until objective disease progression or beyond RECIST v1.1 defined progression if patient is receiving clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria.

Detailed study treatment schedule is shown in the Study Plan (See Table 1).

Following objective disease progression according to RECIST 1.1, as per investigator assessment, patients who were randomized to SoC arm may have the option to receive open-label AZD9291 provided the specific criteria are met, and should the patient wish to do so. For further details on post-progression cross-over to AZD9291 and Study Plan for post-progression cross-over to AZD9291 please refer to Sectio n 4.3.5 and Table 2, respectively.

4.3 Post-Treatment Follow-up period

4.3.1 Discontinuation visit

A Discontinuation visit will be performed at the time the study drug is permanently stopped. Refer to Table 1, Table 2 or Table 3 for details.

4.3.2 Twenty-eight day follow-up

As a minimum, telephone contact should be made with the patient 28 days (+ 7 days) following the discontinuation of study drug to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy). Refer to Section 6.3 for full details on AE recordings during follow-up.

4.3.3 Progression follow-up

Patients who discontinue study drug for reasons other than objective disease progression will continue RECIST v1.1 assessments every 6 weeks (relative to date of randomisation) for objective progression. Patients who continue to receive treatment following objective progression due to clinical benefit will have tumour assessments as per standard local practice, with Investigator assessment of response collected.

In addition to tumour assessments, the following assessments are also required during this follow-up period (up to primary PFS analysis) as detailed in the Study Plan (See Table 1, Table 2).

- WHO Performance Status
- Plasma samples for ctDNA and blood borne biomarkers
- EORTC QLQ-C30
- EORTC QLQ-LC13

- PRO-CTCAE
- Health Resource Use Module
- Concomitant medications
- Adverse event collection
- Anti-cancer and surgical therapies

  After primary PFS analysis the following assessments are not also required during this follow-up period as detailed in the Study Plan (Table 3)

- EORTC QLQ-C30
- EORTC QLQ-LC13
- PRO-CTCAE
- Health Resource Use Module
- Plasma samples for ctDNA and blood borne biomarkers are required only at the time of progression for patients who have not crossed-over.

4.3.4 Survival follow-up (up to final OS analysis)

Assessments for survival should be made every 6 weeks following objective disease progression. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician.

Survival data will be collected up to the time of the final OS analysis in the patients randomised prior to the end of global recruitment. Patients should be contacted in the week following the data cut-off for each analysis of survival (i.e., at the time of primary PFS analysis and final OS analysis) to provide complete survival data.

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

Following the DCO for each planned analysis, a full OS sweep will be conducted. During the OS sweep, each surviving patient, or a close relative, will be contacted for a full collection of survival data, in order to provide the most accurate data for use in OS analyses. During this time, dates of deaths may also be obtained from public records such as death registries.

4.3.5 Cross-over to AZD9291

Following objective disease progression according to RECIST 1.1, as per investigator assessment, patients who were randomized to SoC arm may have the option to receive open-

label AZD9291. The following steps must be performed as specified in order for a patient to be able to receive open label AZD9291.

Central confirmation of disease progression

- Should the investigator determine the patient to have progressed according to RECIST 1.1, images must be sent for central confirmation of disease progression. Progression must be confirmed centrally in order for a patient to be eligible to receive open-label AZD9291. If progression is not confirmed centrally, the patient may continue to receive randomized treatment (should it be in their interests to do so) and have progression assessed by independent central imaging review at a future timepoint.

- progression must occur while on the study treatment or within 28 days of stopping the protocol treatment, without intervening therapy

After IEC/IRB approval of Clinical Study Protocol version 4.0, all patients determined to have objective disease progression as per Investigator's assessment, will be given the opportunity to begin treatment with open-label AZD9291, if eligible; central confirmation of disease progression will no longer be required

Unblinding

- Following independent central confirmation of progression, the patient may then be unblinded to establish randomized treatment. If randomized to SoC treatment arm, the patient may be a candidate to receive open-label AZD9291. Patients who have been unblinded prior to central confirmation of progression are not able to receive open-label AZD9291.

T790M Testing

- In order to be eligible to receive open-label AZD9291, the patient's tumour must have been confirmed as T790M mutation positive from biological material collected post-progression.

- Determination of tumour T790M mutation positive status may be performed locally (without the requirement for a central test), or centrally for those patients unable to be tested locally.

- For local determination of T790M status, a laboratory report confirming tumor T790M status performed in an accredited, certified or quality assured clinical laboratory as required by country-specific guidelines, using an appropriately validated test must be provided

- For central determination, patients are required to provide a minimum of 4 FFPE fixed tissue sections (5µm thickness) from a sample taken post-progression

Open-label treatment with AZD9291

- Once a patient has had independent central confirmation of disease progression, is unblinded, confirmed as randomized to the SoC treatment arm and determined to be T790M mutation positive, they may commence treatment with open-label AZD9291. See Table 2 for details of assessments to be performed.

- Any unresolved toxicities from prior therapy should be controlled, and be no greater than CTCAE grade 1 (with the exception of alopecia which may be grade 2) at the time of starting AZD9291 treatment
- Patients who are eligible and choose to cross-over to AZD9291 treatment will be dispensed bottles of AZD9291 80 mg, once daily tables. For details on AZD9291 please refer to Section 7.2

4.4 Patient management post primary PFS analysis and up to final OS analysis

The primary analysis of PFS will occur when approximately 359 progression events have been observed out of the globally randomised patients (excluding China) and the primary analysis of PFS for China will occur when approximately 82 progression events have been observed in China's cohort.

Following the primary PFS analysis patients still on AZD9291 may continue treatment with AZD9291 as long as they show clinical benefit, as judged by the investigator.

Following the primary PFS analysis patients still on the SoC arm will be given the opportunity to begin treatment with AZD9291 80mg, once daily following objective progression and T790M status confirmation, if it is considered in the patient's best interest by the Investigator and they are eligible to receive AZD9291 (no contraindications and consistent with any available local prescribing information). These patients may continue treatment with AZD9291 as long as they show clinical benefit, as judged by the investigator. If patients are not given AZD9291 at the discretion of the investigator, they will enter into the follow-up phase of the study, and other treatment options should be discussed by the investigator.

Patients on study treatment will be followed for survival and core safety assessments (haematology, clinical chemistry, AEs/SAEs and concomitant medications (including any subsequent cancer therapy), study treatment dosing details as per Table 3.

All patients (both patients still on study treatment and patients withdrawn from study treatment) will be followed for survival, subsequent therapy, status unless consent is withdrawn or patient is lost to follow up.

4.5 Patient management post final OS analysis

The final analysis in the globally recruited population of the study (OS, TFST, TSST and safety endpoints only) will be conducted at approximately 60% maturity. For example; 60% maturity would be achieved when approximately 318 death events (across both arms) have occurred in the planned approximately 530 globally recruited patients. A separate final analysis in the population recruited in mainland China only (OS and safety endpoints only) will also be conducted at approximately 60% maturity (across both arms). For example; 60% maturity would be achieved when approximately 72 death events have occurred in the planned approximately 120 patients recruited in mainland China.

At this time point (6 weeks post DCO), the clinical study database will close to new data. Patients are, however, permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from treatment. Cross-over to AZD9291 will no longer be permitted. If an investigator wishes to treat SoC arm patients with AZD9291 following the final OS analysis, it can be done with marketing supply of AZD9291. Dispensing of study treatment post final OS analysis DCO will be done outside of IWRS. Patients who remain on study treatment after this time point will be monitored according to routine clinical practice as defined by the Investigator. At routine clinic visits, patients will return used and unused medication, and a thorough drug accountability assessment will be performed at the site.

For patients who do continue to receive treatment beyond the time of this data cut off, investigators will continue to report all SAEs, that may be related to AZD9291 to AstraZeneca via paper and emailed (preferably) or faxed directly to TCS DES (also known as AZ DES) in accordance with Section 6.4, 6.5 and 6.6. If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the IP, the investigator should notify AstraZeneca (see Section 6.4). Additionally, as stated in Section 6.3, any SAE or non-serious AE that is ongoing at the time of this DCO, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up.

5. STUDY ASSESSMENTS

The DataLabs® Electronic Data Capture (EDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRF 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 (CSA). The Investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

For details of data and study management see Section 9.4 of the Clinical Study Protocol (CSP).

5.1 Efficacy assessments

5.1.1 RECIST v1.1 (up to Primary PFS analysis)

The imaging modalities used for RECIST v1.1 assessments will be CT or MRI scans of the chest and abdomen (including liver and adrenal glands). The methods used at baseline for assessment of tumour burden (CT or MRI) 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.

Specifically, patients with known or suspected brain metastases at screening should have a CT/MRI of the brain at baseline. Patients with confirmed brain metastases at baseline should be followed up on study with repeated CT/MRI assessment using the same frequency as the other RECIST assessments. The same modality for CT/MRI should be used for a patient throughout the study. Brain metastases will be assessed as non-target lesions.

The baseline assessments should be performed within 28 days prior to study drug initiation. Subsequent assessments are to be performed every 6 weeks (± 1 week) relative to randomisation for the first 18 months (78 weeks) and then every 12 weeks (± 1 week) until objective disease progression as per RECIST v1.1, even if a patient discontinues treatment prior to progression or receives other anti-cancer treatment. It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled visit (± 1 week window interval) and the patient has not progressed, every attempt should be made to 1) perform the subsequent scans at their scheduled time points and 2) collect the nearest scan to the missing visit. Any other sites at which a new disease is suspected should also be appropriately imaged during the study. In general, scans should be performed after ePRO assessments, when possible.

Imaging assessments including unscheduled visit scans should be collected on an ongoing basis and sent to PAREXEL Informatics to enable independent central analyses (see Section 5.1.2). Following objective RECIST v1.1 progression, patients should have tumour assessments as per standard local practice for assessment of PFS2 (Section 5.1.3), and these post RECIST v1.1 progression local-practice scans should not be sent to PAREXEL Informatics.

For Investigator assessment, RECIST v1.1 criteria will be used to assess each patient's tumour response to treatment and allow calculation of PFS, ORR, DoR, DCR, and depth of response. The RECIST v1.1 guidelines for measurable, non-measurable, target and non-target lesions, and the objective tumour response criteria (complete response [CR], partial response [PR], stable disease [SD], or progression of disease [PD]) are presented in Appendix C). See Section 4.2 for considerations related to RECIST v1.1 assessments.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesions (NTLs) or the appearance of a new lesion, it is advisable to

continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If the repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve "unequivocal progression" on the basis of NTLs, there must be an overall substantial worsening in NTLs such that, even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Categorisation of objective tumour response assessment at each visit will be based on the RECIST v1.1 criteria of response: CR, PR, SD, and PD. Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

The primary PFS analysis for this study will be based on the tumour assessments using Investigator's assessments according to RECIST v1.1 and the management of patients will be based solely upon the results of the RECIST v1.1 assessment conducted by the Investigator.

Post the primary PFS analysis, tumour assessment will be performed in accordance with clinical practice and scans will no longer be centrally collected.

5.1.2 RECIST version 1.1 assessment of Blinded Independent Central Review

All imaging assessments, including unscheduled visit scans, will be duplicated and collected on an ongoing basis and sent to PAREXEL Informatics to enable central analysis for BICR. Results of this independent review will not be communicated to Investigators. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to enable central analysis.

The central review must provide confirmation of progression for patients who have tumour progressed, as assessed by the investigator, prior to cross-over to start receiving AZD9291. Otherwise, the results of this independent central review will not be communicated to the investigational site, and the management of patients will be based on the result of RECIST 1.1 assessments conducted by the investigator.

After the primary analysis of PFS no further central collection of scans to assess response by RECIST is required.

5.1.3 Assessment of second progression (up to primary PFS analysis for global and China cohort patients)

Following first objective progression, patients will have their progression status recorded every 6 weeks to assess time to second progression (PFS2) after start of subsequent therapy. A patient's progression status is defined according to the local standard clinical practice and may involve any of: objective radiological (preferred) progression, symptomatic progression, or death. Scans will be performed according to the local practice and formal RECIST measurements will not be collected for assessment of PFS2. The date of PFS2 assessment and Investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF. After the primary analysis of PFS, no further PFS2 assessments will be required along with all other RECIST derived endpoints.

5.1.4 Mandatory screening tumour biopsy sample for central mutation analysis

Tumour sample must be formalin fixed and paraffin embedded (FFPE). Biopsy samples taken from bone metastasis and cytology samples are unsuitable for testing and should not be provided. Samples may be collected from primary or metastatic tumour deposits. Sites should ship the FFPE tumour sample to the testing laboratory as soon as it is available. Blocks must be provided wherever possible. Mandatory provision of an unstained, archived tumour tissue sample in a sufficient quantity to allow for central analysis of EGFR mutation status and retrospective testing of T790M should be provided.

The Investigator will be asked to provide:

- Formalin-fixed, paraffin-embedded tumour tissue blocks, or
- A minimum of 8, but when available, 12 re-cut unstained sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section is to be 5 μm thick.

The mandatory screening tumour biopsy must not be taken from a previously irradiated lesion. The biopsy must not be taken from the lesion(s) selected for inclusion criterion # 9 (unless only one measurable lesion exists, in which case the baseline tumour assessment scans are to be done at least 14 days after the screening biopsy). This biopsy sample is not subject to the 28-day screening window; if tissue is already available from a biopsy taken since confirmation of disease progression to Stage IIIB or Stage IV, then there is no need for a further biopsy as this sample can be submitted for EGFR mutation status and T790M testing. If the first biopsy submitted for central testing is not confirmed as EGFR mutation positive (i.e., due to test failure), a further biopsy sample may be submitted for central testing. Central re-tests on a new sample can only be performed if the original testing failed; re-tests are not permitted if the central EGFR testing result is EGFR mutation negative, or does not report an EGFR eligible mutation (Exon 19 Deletion or L858R). Patients who have been locally tested as EGFR negative maybe submit their tissue biopsy for testing at the central laboratory at the discretion of the Investigator.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (See Table 1, Table 2 and Table 3).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date and results (values, units, and reference ranges) will be recorded on the appropriate eCRF. The clinical chemistry, haematology, and urinalysis will be performed at a local laboratory at or near to the Investigator site. If clinical chemistry, haematology, and urinalysis assessments have been performed within 14 days pre-randomisation, they do not have to be repeated prior to commencing treatment on Visit 2 Day 1 if the patient's condition has not changed (i.e., no new treatment during this period of time, no new complication, or aggravation). Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. The number of samples/blood volumes is therefore subject to site-specific change.

The following laboratory variables will be measured (Table 4):

Table 4 Laboratory safety variables

Clinical chemistry	**Haematology**
S/P-Albumin	B-Haemoglobin
S/P-ALT	B-Leukocyte
S/P-AST	B-Haematocrit
S/P-Alkaline phosphatase	B-RBC count
S/P-Bilirubin, total	B-Absolute leukocyte differential count:
S/P-Calcium, total	Neutrophils
S/P-Creatinine	Lymphocytes
S/P-Glucose (fasting, on PK days only) [a]	Monocytes
S/P-LDH[b]	Basophils
S/P-HbA1C	Eosinophils
S/P-Magnesium	B-Platelet count
S/P-Potassium	B-Reticulocytes
S/P-Sodium	**Urinalysis**
S/P-Urea nitrogen/BUN	U-Glucose
	U-Protein
	U-Blood

ALT = alanine aminotransferase; AST = aspartate aminotransferase; B = blood; BUN = blood urea nitrogen; HbA1C = hemoglobin A1C; LDH = lactate dehydrogenase; P = plasma; PK = pharmacokinetics; RBC = red blood cells; U = urine; S = serum.

[a] Patients will be required to fast (water only) for at least 8 hours prior to the collection of a fasting glucose sample required on PK days. Random glucose sample will be collected on non-PK days.

[b] LDH is an additional variable collected at Visit 1 only.

Additionally, at the Screening Visit, a pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) will be collected from all women of child-bearing potential only.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the site as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

Note: In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥2xULN, please refer to Appendix D 'Actions required in cases of combined increase of aminotransferase and total bilirubin (Hy's Law),' for further instructions (Section 6.3.7 and Appendix D).

5.2.1.1 Volume of blood

Total mandatory blood volume in the first 10 weeks is approximately317 mL (Table 5).

Table 5 Blood sample volumes

Visit	Safety (mL)[a]	PK analysis (mL)[b]	Plasma (mL)	PGx (mL)
Screening	15	NA	20	10 (optional)[c]
Cycle 1	45	6 (3 x 2 mL)	90	
Cycle 2	15	NA	30	
Cycle 3	15	6 (3 x 2 mL)	30	
Cycle 4 (onwards)	15	NA[b]	30	
SUBTOTAL at Cycle 4 (mandatory)	**105**	**12**	**200**	**NA**

NA = not applicable; PGx = pharmacogenetics; PK = pharmacokinetics.

[a] For safety, assumes 6 mL clinical chemistry and 9 mL haematology per visit. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. The number of samples/blood volumes is therefore subject to site-specific change.

[b] Only taken every other cycle up to Cycle 13.

[c] If for any reason the sample is not drawn prior to dosing, it may be taken at any visit until the last study visit.

5.2.2 Physical examination, height, and weight

All patients will have a physical examination performed and weight assessed at the time points indicated in the Study Plan (See Table 1, Table 2 and Table 3), which includes an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculoskeletal

(including spine and extremities), and neurological systems. Weight will be documented in kilograms (e.g., 68.5 kg) in eCRF. Height will only be measured during the Screening period, and it will be documented in centimeters (e.g., 168 cm) in the eCRF.

5.2.3 Electrocardiogram

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. For each time point, indicated in the Study Plan (Table 1, Table 2 and Table 3), 3 ECG recordings should be taken at about 5 minute intervals. A standardised ECG machine should be used (which will be provided by the Sponsor), and the patient should be examined using the same machine throughout the study if possible.

After paper ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent medical history condition. For all ECGs details of rhythm, ECG intervals, and an overall evaluation will be recorded.

Prior to Primary PFS analysis, ECG data will be collected digitally and will be transferred electronically for central analysis as described in the study specific ECG manual. (There is a potential to move from centrally reviewed to locally reviewed ECGs upon review of QT data of approximately 100 patients). The investigator may choose to perform a non-digital ECG at the time of the screening visit in order to identify patients eligible for study entry. If a non-digital ECG is performed at the screening visit it cannot subsequently be used as a baseline recording, in this situation an ECG will need to be collected on the baseline visit in digital form.

Heart rate, PR, R-R, QRS, and QT (QTcF) intervals will be determined and reviewed by an external cardiologist.

If there is a clinically significant abnormal ECG finding during the Treatment period, this should be recorded on the AE eCRF, according to standard adverse events collection and reporting processes. A 28-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.

After the primary analysis, ECG assessments will be performed locally (triplicate 12-lead ECG, with paper printouts of 10 seconds for Investigator review) and a paper copy will be stored in the patient's medical records. ECG information (evaluation of normal/abnormal) will continue to be recorded in the eCRF. If there is a clinically significant abnormal ECG findings during this period, this should be recorded on the AE eCRF, according to standard adverse events collection and reporting processes. After final OS analysis, ECG assessments will be performed according to routine clinical practice as defined by the Investigator.

5.2.4 Echocardiogram/multigated analysis scan

An echocardiogram or MUGA scan to assess LVEF will be performed at screening and at the visits as shown in the Study Plan (See Table 1,Table 2 and Table 3). The screening echocardiogram or MUGA to be considered as the baseline. A new echocardiogram, or MUGA will be performed if any clinical significant cardiological changes have occurred between the last Echo exam and the initiation of the study at investigators discretion. The modality of the cardiac function assessments must be consistent throughout the study, i.e., if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans. The patients should also be examined using the same machine and operator whenever possible and quantitative measurements should be taken.

After final OS analysis, the assessment will be performed as clinically indicated necessary by the Investigator.

5.2.5 Vital signs

5.2.5.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured after 10 minutes rest. Assessments will be performed at the visits as shown in the Study Plan (See Table 1, Table 2 and Table 3) and additionally at the discretion of the Investigator if clinically indicated.

Any changes in vital signs (pulse and BP) should be recorded as an AE if applicable.

5.2.6 Adverse events

All AEs that occurred after signing the ICF until 28 days after the last dose of study drug will be monitored and recorded in the eCRF. See Section 6 for detailed description and reporting of AEs and SAEs.

5.2.7 Other safety assessments

5.2.7.1 Ophthalmologic exam

At screening, a full ophthalmic assessment (measurements of best-corrected visual acuity, intraocular pressure, and slit-lamp fundoscopy) should be performed. Patients who experience any visual symptoms (including blurring of vision), additional tests may be conducted throughout the study period, if clinically indicated.

Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings. These photographs should be available for central review by AstraZeneca and AstraZeneca representatives if necessary.

Ophthalmology examination results should be collected in the eCRF.

5.3 Other assessments

5.3.1 WHO Performance Status

Performance status will be assessed at the scheduled visits indicated in the Study Plan (See Table 1, Table 2) according to WHO criteria as follows:

- 0 = Fully active, able to carry out all pre-disease activities without restrictions.
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
- 2 = Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.

5.3.2 Record concomitant medication use

Information on any treatment within the 4 weeks prior to initiation of study drug and all concomitant treatments given up to 28 days after discontinuation of study treatment, or objective disease progression (whichever is later), with reasons for the treatment, will be recorded in the eCRF. Please refer to Section 7.7.

5.3.3 Anti-cancer and surgical treatments

All prior anti-cancer and surgical therapies will be collected at screening and throughout the study as indicated on Table 1, Table 2 and Table 3. These will be recorded in the eCRF.

5.3.4 Patient Reported Outcomes

Patient Reported Outcomes, an umbrella term referring to all outcomes and symptoms, are directly reported by the patient. Patient Reported Outcomes have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered: EORTC QLQ-C30, EORTC QLQ-LC13, CTSQ-16, and PRO CTCAE (See Appendix E).

Patient Reported Outcomes will be collected for all patients throughout the study period via a hand-held electronic device. See Study Plan (See Table 1, Table 2) for the timing of collection. Patient Reported Outcomes will not be collected post PFS analysis (see Table 3)

The PROs must be completed prior to randomisation, before any other study procedures once eligibility is confirmed and informed consent has been given. In general, the ePRO instruments should be administered prior to any and all treatment assessment (i.e., including scans for tumour assessment). Where it is not possible to follow this guidance, the timing of the tumour assessment should be prioritised over the assessment of ePRO. Questionnaires are available on electronic devices (LogPads) for a period of up to 5 days for each assessment (i.e., it will be available two days before the designated “Study Day” and two days after the

designated "Study Day") for completion. Questionnaires may be completed one time within the 5-day period of availability. ePRO completion is mandatory to those sites that have it approved. In case a patient is not eligible to complete the ePROs e.g., due to sight impairment, illiteracy, sites are required to still assign the LogPad and then immediately perform the "End LogPad Use", so that this is recorded in the database.

5.3.4.1 EORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993. It consists of 30 items and measures cancer patients' functioning (HRQoL) and symptoms (Aaronson et al 1993) for all cancer types. Questions can be grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social); 3 multi-item symptom scales (fatigue, pain, nausea, and vomiting); a 2-item global HRQoL scale; 5-single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea) and 1 item on the financial impact of the disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population.

The EORTC QLQ-LC13 is a well-validated complementary module measuring lung cancer associated symptoms and side effects from conventional chemotherapy and radiotherapy (Bergman et al 1994). Refer to Appendix E. The EORTC QLQ-LC13 includes questions assessing cough, haemoptysis, dyspnea, site specific pain (symptoms), sore mouth, dysphagia, peripheral neuropathy, and alopecia (treatment-related side effects) and pain medication.

Both EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires will be administered in all participating countries in this study.

5.3.4.2 Cancer Therapy Satisfaction Questionnaire-16 items (CTSQ-16)

The CTSQ-16 is a validated 16-item questionnaire measuring 3 domains related to patients' satisfaction with cancer therapy: Expectations of Therapy (ET), Feelings about Side Effects (FSE), and Satisfaction with Therapy (SWT). The CTSQ-16 was developed for use in a wide range of cancer types and stages, and is specific to adult patients receiving cancer therapy. In particular, this instrument can be used for both intravenous (IV) and oral cancer therapy assessments (See Appendix E). The CTSQ-16 will only be administered in those countries where a linguistically validated version exists. Day 43 visit (i.e.,Cycle 3, Day 1 visit) should be scheduled close to Day 43 (±2 days), so that ePROs can be completed before the scan. Where it is not possible to follow this guidance, the timing of the tumour assessment should be prioritised over the assessment of ePRO.

5.3.4.3 Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Event approximately 17 items (PRO-CTCAE)

The PRO-CTCAE system has been developed by the National Cancer Institute (NCI). The PRO-CTCAE will only be administered in those countries where a linguistically validated version exists, currently English, Japanese, Spanish, and German (both the English and Spanish versions are suitable for global use where these languages are spoken). The PRO version of the CTCAE is an item-bank of symptoms experienced by patients while undergoing

treatment of their cancer. It was developed in recognition that collecting symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings (Sprangers & Aaronson 1992; Litwin et al 1988; Basch et al 2009). To date, 81 symptoms of the CTCAE v4 have been identified to be amenable to patient reporting. These symptoms have been converted to patient terms (e.g., CTCAE term "myalgia" converted to "aching muscles"). For several symptoms, like fatigue and pain, additional questions are asked about symptom frequency, severity, and interference with usual activities. For other symptoms like rash, additional questions focus on the presence on the body. The items included in the PRO-CTCAE have undergone extensive qualitative review among experts and patients. Using cognitive testing methods, these items and the additional questions for some of the symptoms have been extensively evaluated by cancer patients, so that symptoms of interest are clear, comprehendible, and measurable. Not all items are administered in any one clinical trial. The intention is to only ask patients to complete those items, which are considered relevant for the trial, site of cancer, and cancer treatment (See Appendix E). For this study, only 17 items are considered relevant for this cancer treatment, i.e., rash, skin dryness, acne, itching, nail loss, nail ridging, nail discoloration, sensitivity to sunlight, decreased appetite, nausea, vomiting, diarrhoea, fecal incontinence, fatigue, blurred vision, mouth/throat sores, and nosebleeds.

5.3.4.4 Administration of electronic Patient Reported Outcomes

Patients will complete the PRO assessments by using a handheld electronic device (ePRO). The following best practise guidelines should be followed when collecting PRO data via an electronic device:

- Site staff to explain the value and relevance of participation to patients that we are asking these questions because we are interested in hearing directly from them how they feel. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the patient has any medical problems he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.

- Remind patients that there are no right or wrong answers; avoid bias by not clarifying items.

- Train the patient on how to use the ePRO device using the materials and training provided by the ePRO vendor. Also provide guidance on whom to call if there are problems with the device by providing the patient information pamphlet provided by the ePRO vendor.

Monitor compliance: minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early. If compliance drops below 85%, a check-in call from the site to ask the patient if he/she has any difficulties is highly recommended.

5.3.4.5 Health Resource Use Module

Healthcare Resource Use Module will be completed by the investigational site for any healthcare resource use between visits. The site will ask patients for any health resource use between visits (i.e., excluding routine follow-up clinic visits associated with the clinical trial but including both planned and unplanned admissions) every 6 weeks during the study (including during the Treatment period and the survival follow-up period), at Discontinuation visit, and at progression (if patient has not already discontinued).

For the purposes of economic evaluation, it is necessary to capture healthcare resource use related to the treatment and the underlying disease. Within the study, the following resource use will be captured:

- Hospital episodes including the type of contact (hospitalisations, outpatient, day case), reason, length of stay (including intensive care unit), and concomitant medications and procedures.
- Symptoms for admission.

The above resource use data will mainly come from the patient's medical record and will be captured by site staff using EDC.

After IEC/IRB approval of Clinical Study Protocol version 4.0, healthcare resource use information will not be collected.

5.4 Pharmacokinetics

5.4.1 Collection of samples for randomised patients

Pharmacokinetics blood sampling (2 mL each) will be performed for all patients at pre-dose, 0.5 to 2 hours, and 3 to 5 hours post-dose on Day 1 Cycle 1, and every other cycle thereafter up to and including Cycle 13. Dose time information must be collected on both the day of PK sampling (to determine the exact times of the post-dose PK samples), AND the day immediately prior to PK sampling (to allow the pre-dose PK sample to be used). The date and time of collection of each sample and the date and time of dose will be recorded. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

5.4.2 Determination of drug concentration

Samples for determination of AZD9291 (and metabolite) concentrations in plasma will be collected and analysed by Covance on behalf of AstraZeneca. Full details of the analytical method used will be described in a separate bioanalytical report. All samples still within the known stability of the analytes of interest (i.e., AZD9291, AZ5104, and AZ7550) at the time of receipt by the bioanalytical laboratory will be analysed.

In addition, the PK samples may be subjected to further analyses by AstraZeneca in order to further investigate the presence and/or identity of additional drug metabolites and correlate PK with other primary, secondary, and exploratory endpoints in patients treated with AZD9291.

Any results from such analyses will be reported separately from the Clinical Study Report (CSR).

Details on sample processing, handling, shipment, and storage are provided in the Laboratory Manual.

Full details of the analytical method used will be described in a separate bioanalytical report.

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of or destroyed and anonymised by pooling after the bioanalytical report finalization or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless requested for future analyses.

Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a bioanalytical report.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AstraZeneca assigned Biobank; see details in the Laboratory Manual).

5.5 Pharmacodynamics (not applicable)

5.6 Pharmacogenetics

If a patient agrees to participate in the host pharmacogenetics research component of the study, a blood sample will be collected.

AstraZeneca intends to perform genetic research in the AZD9291 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD9291.

The benefits of being able to explore associations between genes and clinical outcomes within the AZD9291 programme are potentially many and include:

- analysis of genes that may affect efficacy, safety, and tolerability (for example, but not limited to, drug metabolising enzymes and drug transporters).
- genetic research into genes that may contribute to the development of, or susceptibility to NSCLC.

The results of this pharmacogenetic research will be reported separately and will not form part of the CSR.

5.6.1 Collection of pharmacogenetic samples

The patient's consent to participate in the pharmacogenetic research components of the study is optional.

The single blood sample (10 mL) for genetic research will be obtained from the patients prior to the first administration of AZD9291 in the study. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE. Such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn prior to dosing, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

5.6.2 Storage, re-use, and destruction of pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of the last patient last visit (LPLV), after which they will be destroyed. Deoxyribonucleic acid is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

Refer to Appendix F for details of the optional (DNA) genetic research.

5.7 Exploratory research

CCI

[redacted]

CCI

[redacted]

[redacted]

5.8 Management of biological samples

5.8.1 Storage, re-use, and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the LPLV, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR 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.

5.8.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix G' International Air Transport Association (IATA) 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment, and containment provisions are approved.

All tumour samples should be shipped at ambient temperature as per the Laboratory Manual directly to the testing laboratory. Tumour material for T790M testing may be sent to the AstraZeneca assigned Biobank for storage prior to retrospective analysis.

5.8.3 Chain of custody of biological samples

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

The Principal Investigator, at each site, keeps full traceability of collected biological samples from the patients while in storage at the site 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.

Samples retained for further use are registered in the AstraZeneca assigned Biobank during the entire life cycle.

5.8.4 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Where collection of the biological samples is an optional part of the study, then the patient may withdraw consent for the use of these samples and continue in the study.

The Principal Investigator:

- Ensures patient's withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.

- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented.
- Ensures the laboratory(ies) 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 patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and signed document returned to the study site.

AstraZeneca ensures that biological samples are destroyed at the end of a specified period as described in the informed consent.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study is 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). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that 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 patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix H of the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events in the eCRF

Adverse Events will be collected from the time of signature of informed consent throughout the Treatment Period and safety follow-up and to the end of the overall survival follow-up. The safety follow-up period is defined as 28 days after study drug is discontinued. Serious AEs should be reported to AstraZeneca (see Section 6.4).

For each patient who discontinues study drug for any reason, but still participating in the trial:

- Follow-up information on all ongoing AEs should continue to be collected to the end of the survival follow-up.
- Serious AEs considered related to study procedures must continue to be collected and reported to AstraZeneca using standard SAE timelines and process until the end of survival follow up
- All deaths must continue to be collected on the death eCRF page until the end of the survival follow-up.

After the final OS data cut-off, there may be some subjects remaining on study treatment. For these subjects who are continuing to receive AZD9291 AstraZeneca will collect information (during the treatment period and for 28 (+ 7) days after last dose) on SAEs, overdose and pregnancy (as per Section 6.6) via paper and emailed (preferably) or faxed directly to TCS DES (also known as AZ DES). Drug accountability information will be recorded in the patient notes.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. 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.

6.3.3 Variables

The following variables will be collected for each AE:

- Adverse event (verbatim)
- The date when the AE started and stopped

- Changes in CTCAE grade (for skin reactions and diarrhoea only); maximum CTCAE grade for all other AEs
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Adverse event caused patient's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious SAE
- Date Investigator became aware of SAE
- Adverse event is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Description of SAE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between IP and each AE, 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.'

A guide to the interpretation of the causality question is found in Appendix H to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to the recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs (pulse and BP) will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated parameters should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP unless clearly due to progression of disease under study (See Section 6.3.8).

If deterioration in a laboratory value, vital sign, ECG, or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Hy's Law

Cases where a patient shows an AST or ALT ≥3xULN or total bilirubin ≥2xULN may need to be reported as SAEs. Prompt reporting of cases meeting Hy's law criteria (via the SAE

expedited reporting system) is required for compliance with regulatory guidelines. The Investigator is responsible for, without delay, determining whether a patient meets potential Hy's Law criteria.

Details of identification of Hy's Law cases and actions to take are detailed in Appendix D.

6.3.8 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.3.9 Disease under study

Symptoms of DUS are those which might be expected to occur as a direct result of locally advanced unresectable NSCLC. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the investigational product

6.3.10 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study drug and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

6.3.11 Handling of deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of study drug, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module, but should not be reported as a SAE during the study.
- Where death is not clearly due to disease progression of the disease under study, the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.
- Deaths with an unknown cause should always be reported as a 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

(with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the study drug, or to the study procedure(s) until the time of study completion. All SAEs will be recorded in the eCRF.

At the time of study completion (i.e. after the final DBL), the WBDC system will be decommissioned and SAE data will be collected via paper and emailed (preferably) or faxed directly to TCS DES (also known as AZ DES), which will be responsible for processing all SAEs onto the AZ global safety database. Drug accountability information will be stored in the patient notes at site.

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

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs 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 1 calendar day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug, AZD9291 and the European Union (EU) Summary of Product Characteristics (SPC) for the active comparator product (including any AstraZeneca comparator).

If an investigator learns of any SAEs, including death, at any time and he/she considers there is a reasonable possibility that the event is related to AZD9291, the investigator should notify

AstraZeneca. Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

6.5 Overdose

Investigators are advised that any patient, who receives a higher daily dose than intended should be monitored closely, managed with appropriate supportive care, and followed up expectantly.

Such overdoses should be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca IP occurs in the course of the study, then the Investigator or other site personnel inform the appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca during the study and within 6 weeks of the last dose of IP.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be followed up and documented. To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first IP dose and within 4 months after the last IP dose should be followed up and documented.

6.7 Management of investigational product-related toxicities

Dose reduction levels for AZD9291, gefitinib, and erlotinib are provided in Table 6. Gefitinib has no lower dose available.

Table 6 Dose reduction levels

	AZD9291	Gefitinib	Erlotinib
Starting dose	80 mg AZD9291/ comparator matching placebo	250 mg gefitinib/ AZD9291 matching placebo	150 mg erlotinib/ AZD9291 matching placebo
Reduced dose	40 mg AZD9291/ comparator matching placebo	250 mg gefitinib[a]/ AZD9291 matching placebo	100 mg erlotinib/ AZD9291 matching placebo

a No dose reduction for gefitinib is actually possible. Reduced dose for gefitinib is the same as the starting dose as 250 mg tablets are the lowest dose available.

6.7.1 General dose adjustments for adverse events

All patients to commence treatment at the starting dose level as shown in Table 6.

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, 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 1 within 2 weeks of onset, study drug may be restarted at the same dose (starting dose) or reduced dose using the dose reduction levels in Table 6 and with discussion and agreement with the AstraZeneca Study Team Physician as needed. If restarting at the same dose level, patients should be closely monitored for 3 days

following the restart of treatment. If within 3 days there is recurrence of same toxicity, a dose reduction should be considered at the Investigator's discretion.

If the toxicity does not resolve to ≤CTCAE grade 1 after 2 weeks, then the patient should be withdrawn from the study treatment and observed until resolution of the toxicity. There will be no individual modifications to treatment schedule in response to toxicity, only potential dose reduction or dose interruption.

If an AE subsequently requires dose interruption, study drug may restart at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the investigator as described above.

6.7.2 Skin reactions

It is recommended that all patients follow a program of sun protective measures while receiving study drug and for 3 to 4 weeks after discontinuing study drug.

The aim is to reduce the risk of development of skin reactions or minimise the severity of skin reactions and minimise the requirement for dose reduction of study drug. If a patient develops a skin reaction, a variety of agents can be used. These include mild to moderate strength steroid creams, either topical or systemic antibiotics, topical of systemic antihistamines, and retinoid creams, as seen appropriate by the Investigator upon assessment of the skin reaction. Immediate symptomatic treatment should be provided.

Skin reactions are to be reported as AEs in the eCRF, with additional details captured in the "SKNREAC" eCRF such as:

- Changes in the characteristics of skin reactions will be collected in the "SKNREAC" eCRF.
- Changes in the CTCAE grade of skin reactions will be collected in the AE eCRF.
- Photographs of skin reactions may be collected and these photographs should be available for central review by AstraZeneca and for external expert dermatological review, if required.
- Skin biopsies of skin reactions may be taken.

6.7.3 Gastrointestinal toxicities

Nausea, vomiting, or both may be controlled with anti-emetic therapy.

6.7.4 QTc prolongation

Patients with QTc prolongation (i.e., confirmed QTc prolongation to >500 msec absolute or a >60 msec increase from baseline) should have study drug interrupted and regular monitoring of ECGs performed until resolution to baseline. If the toxicity resolves or reverts to ≤CTCAE grade 1 within 3 weeks of onset, study drug may be restarted at the same dose or reduced dose using the dose reduction levels in Table 6 with discussion and agreement with the AstraZeneca Study Team Physician as needed. If the toxicity does not resolve to ≤CTCAE grade 1 within 3 weeks, the patient will be permanently withdrawn from study drug. Study

treatment must be permanently discontinued in patients who develop QTc interval prolongation in combination with any of the following: Torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia.

Following study treatment initiation if it is considered essential for patient management to give drugs known to prolong QTc interval, regardless of TdP risk category in the ArizonaCert (which categorizes drugs based on the risk of inducing TdP; https://crediblemeds.org/), close monitoring with ECGs and electrolytes is recommended.
Close monitoring with ECGs and electrolytes is also recommended in patients with congestive heart failure, and/or electrolyte abnormalities

6.7.5 Interstitial lung disease

If a new or worsening of pulmonary symptoms (e.g.dyspnoea) or occurrence of a radiological abnormality suggestive of ILD is observed, an interruption in study drug dosing is recommended, and the Study Physician 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 (HRCT), blood and sputum culture, haematological parameters) will be captured by eCRF. All image data should be provided to AstraZeneca. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and study drug must be permanently discontinued. In the absence of a diagnosis of ILD, study drug may be restarted following consultation with the Study Physician.

Note: Patients experiencing ILD will not be permitted to restart study drug.

6.7.6 Keratitis

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

6.8 Study governance and oversight

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be convened, and will meet initially when approximately 100 patients have been randomised and followed up for 3 months (estimated to be 6 months from first patient randomised). Thereafter, the IDMC will conduct further reviews of safety data, for example; when global recruitment ends (estimated to be approximately 15 months from first patient randomised). Further meetings for review of safety data and supportive efficacy data from all patients may be convened at the discretion of the IDMC at any time until the primary analysis, to evaluate whether the trial should be stopped due to potential harm to patients.

The IDMC will review safety and supportive efficacy assessments and make recommendations to continue, amend, or stop the study based on findings. Serious adverse events, adverse events, and other safety data will be reviewed, and individual and aggregated safety data will be evaluated by the IDMC. Note no alpha adjustment is required for the IDMC data assessment as the stopping boundary would allow for ruling out harm only. Full details of the number of progression events, number of patients and boundary hazard ratio to determine stopping for harm will be documented in the IDMC Charter prior to the first IDMC safety review meeting. The boundary will not be considered binding and will be used in addition to the accumulating available safety data to decide whether to continue the trial as planned, stop or modify the trial.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational products

AstraZeneca will supply AZD9291 as tablets for oral administration as a single daily dose of 80 mg. Given the need for blinded comparators (gefitinib/erlotinib), AstraZeneca will source all comparators and develop matching placebos. Gefitinib and erlotinib will be supplied as tablets for oral administration as a single daily dose with doses indicated in Table 7.

Tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Bottles will be dispensed to patients in the AstraZeneca packing provided. The packaging includes bottles, caps, and a label. Bottle tampers should not be broken prior to dispensing the study drug to a patient.

Table 7 Identity of investigational products

Investigational product	Dosage form and strength
Test product	
AZD9291	40mg tablets 80mg tablets
Comparator [a]	
Gefitinib	250 mg tablets
Erlotinib	150 mg tablets 100 mg tablets
Placebo	
AZD9291-matching placebo	NA
Gefitinib-matching placebo	NA
Erlotinib-matching placebo	NA

[a] Comparator will be pre-selected by the site before site initiation. Gefitinib will not be an option for the United States (USA) sites as this is not approved in the USA. Japan sites will only use gefitinib.

7.2 Dose and treatment regimens

At each dispensing visit, sufficient study drug treatment for 21 days (Cycle 1 to Cycle 7), 42 days (Cycle 7 to primary analysis) or 84 days (from primary analysis onward), plus coverage, will be distributed. Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS. Dispensing of study treatment post final OS data cut-off will be completed outside of the IVRS/IWRS system.

Patients should swallow 2 tablets (1 active drug and 1 placebo) once daily, commencing on Cycle 1 Day 1. Tablets should be taken whole with water.

The initial dose of AZD9291 80 mg once daily can be reduced to 40 mg once daily, and the initial dose of erlotinib 150 mg once daily can be reduced to100 mg once daily under circumstances described in Section 6.7.1. The initial dose for gefitinib (250 mg once daily) cannot be reduced to a lower dose. The dose of gefitinib may be withheld or discontinued if clinically indicated at the discretion of the Investigator.

On site visit days on which PK samples are scheduled, the dosing should be delayed until arrival at the site. Patients should not take their dose until instructed to do so by site personnel.

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 should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their study drug, they should not make up for this dose, but should take the next scheduled dose.

Prior to the final OS data cut-off, any change from the dosing schedule, dose interruptions, or dose reductions should be recorded in the eCRF. Post final OS DCO, drug accountability information will be stored in the patient medical records at the site.

For the SoC patients who are eligible and choose to cross-over to AZD9291, AstraZeneca will supply at each visit AZD9291 as tablets for oral administration as a single daily dose of 80 mg sufficient amount for 21 days treatment plus coverage (cycle 1-6) and 42 days (cycle 7 and onwards) treatment plus coverage. Patient in the cross-over arm should swallow 1 tablet of AZD9291 once daily. Tablets should be taken whole with water.

The initial dose of AZD9291 80 mg once daily can be reduced to 40 mg once daily under the circumstances described in Section 6.7.1.

Additional information about AZD9291 may be found in the Investigator's Brochure. Additional information about gefitinib and erlotinib may be found in their respective EU SPC local prescribing information.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text will be translated into local language.

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

7.4 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.

7.5 Compliance

Prior to the final OS data cut-off, the administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF. Reasons for dose interruption, reduction, or omission will also be recorded in the eCRF. This information plus drug accountability for all study drugs at every cycle will be used to assess compliance with the treatment. Post final OS DCO, drug accountability information will be stored in the patient notes at the site.

Subjects should return all unused investigational product and empty containers to the investigator.

7.6 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 drug dispensed to and returned from the patient.

The study personnel at the investigational site will account for all study drugs received at the site, unused study drugs, and for appropriate destruction. Certificates of delivery and destruction should be signed.

7.7 Concomitant and other treatments

Information on any treatment within the 4 weeks prior to initiation of study drug and all concomitant treatments given up to 28 days after discontinuation of study treatment, or objective disease progression (whichever is later), with reasons for the treatment, will be recorded in the eCRF. Following discontinuation of study treatment, subsequent regimens of anti-cancer therapy will be recorded in eCRF. Please see Section 3.8 for restricted concomitant medications during the study.

Following the primary PFS analysis, only subsequent regimens of anti-cancer therapy will be recorded in the eCRF.

Other anti-cancer therapies, investigational agents, and radiotherapy should not be given while the patient is on study drug.

Pre-medication will be allowed after, but not before, the first dose of study drug. This includes management of diarrhoea, nausea, and vomiting, which should be administered as directed by the Investigator.

Blood transfusions are allowed at any time during the study.

Granulocyte-colony stimulating factors (G-CSF) should not be used prophylactically during Cycle 1. Use of prophylactic G-CSF may be considered after Cycle 1 following discussion with the AstraZeneca Study Team Physician.

Patients may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases. Patients may also receive palliative radiotherapy for painful bony metastases, as long as it will not affect the target and non-target lesions being assessed.

Drugs known to prolong QTc interval:

Current information on drugs known to prolong QTc interval can be found on the Arizona Center for Education and Research on Therapeutics and The Critical Path Institute website:https://crediblemeds.org/research-scientists/

The website categorises drugs based on the risk of inducing Torsades de Pointes (TdP).

The drugs that patients are currently prescribed should be checked opposite the ArizonaCert website.

Following study treatment initiation if it is considered essential for patient management to give drugs known to prolong QTc interval, regardless of TdP risk category, close monitoring with ECGs and electrolytes is recommended.

7.7.1 Other concomitant treatment

Concomitant medications, other than that described above, which are considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

7.8 Post-study access to study drug

Subjects receiving AZD9291 at the time of study completion (ie, after final OS data cut-off date) may continue to receive AZD9291, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment. Study treatment will continue until a study discontinuation criterion (eg, withdrawal of consent, adverse event, clinical progression, or no longer deriving benefit) has been met as assessed by the investigator. Investigators will report all SAEs, overdose and pregnancy to the sponsor until 28 days after receipt of their last dose of study treatment. Post final OS analysis data cut-off, recording and

follow up of SAEs will be done via paper. Drug accountability data will also be collected. Assessments will revert to standard of care at their particular site.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalised around the time of first patient in (FPI). The aim of the study is to compare the efficacy and safety of AZD9291 versus a SoC EGFR-TKI.

The primary analysis for the globally recruited population will be performed when approximately 359 PFS events have occurred. The secondary endpoints of OS in the overall global population will be tested after the primary PFS analysis in a hierarchical procedure at the time of the PFS analysis (and a second final time point when the maturity for OS is approximately 60%). Other secondary efficacy endpoints will be analysed at the time of the PFS analysis, including ORR, DoR, DCR and depth of response.

The final OS analysis in the globally recruited population of the study (OS, TFST, TSST and safety endpoints only) will be conducted at approximately 60% maturity. For example; 60% maturity would be achieved when approximately 318 deaths (across both arms) have occurred in the planned approximately 530 globally recruited patients. The alpha will be split between the two OS analyses to provide strong control of the family-wise Type I error rate (5% 2-sided). This final OS analysis will be summarised in a final addendum to the CSR.

In addition, separate analyses will be conducted for the population of patients recruited in mainland China only, the China-only cohort. The primary analysis will occur at approximately the same PFS maturity to that conducted in the global population. This primary analysis will evaluate the same primary and secondary endpoints as in the primary global analysis. A final analysis of OS will also be performed in the China-only cohort at approximately 60% maturity across both arms.

Alpha Spending and multiple testing strategy

In order to describe the nature of the benefits of AZD9291 treatment, PFS, OS, ORR, DoR, DCR and depth of response will be tested at a 2-sided significance level of 5%.

However, in order to strongly control the type I error at 5% 2-sided, a multiple testing procedure will also be employed across the primary endpoint and secondary endpoints intended for key label claims (i.e. PFS, and OS). There is no requirement to adjust for multiplicity due to PFS interim analyses, since there are no planned interim PFS analyses with the opportunity to make an early claim of effiacy.

To provide strong control of the type I error rate, α=0.05 (two-sided), the primary endpoint of PFS, and endpoints of OS and CNS PFS, will be tested in this sequential order. If any

previous analysis in the sequence is not statistically significant, the alpha will not be transferred to subsequent analyses.

The analyses of PFS, OS and CNS PFS endpoints will occur at the time of the primary analysis of PFS. If the OS analysis is statistically significant at the time of the PFS analysis or the final OS analysis, then the significance testing of CNS PFS will be performed at the full α=0.05 significance level (two-sided). If the OS analysis is not statistically significant at the time of the PFS analysis or the final OS analysis then the significance testing of CNS PFS in will be not be performed.

One analysis of the primary endpoint (PFS) is planned. Two analyses of OS are planned; one interim at the time of PFS and a final analysis. The final OS analysis is planned to be conducted when the OS data is approximately 60% mature (approximately 318 deaths).

A 2-sided 5% alpha will be used in all testing, with the exception of overall survival endpoint. Since two analyses of OS are planned, the Lan DeMets approach that approximates the O'Brien and Fleming spending function will be used to maintain an overall 2-sided 5% type I error across the two planned analyses of OS.

The significance level for the OS analyses will be calculated using the statistical software package EAST by specifying the information fraction for each analysis. The information fraction is calculated as the number of OS events at the analysis time-point divided by the total number of events at the final analysis time-point. For example, assuming a median OS on the SoC arm of 25 months and a median OS of 29 months on the AZD9291 arm, that 140 OS events were observed at the first analysis, the information fraction would be entered as 0.44 (140/318 events) for the first analysis since 140 events are expected at the interim analysis. This would result in a significance level for the first analysis of 0.001 (2 sided) and a significance level for the final analysis of 0.0496 (2-sided).

Any non-statistically significant OS analyses at the time of the primary analysis of PFS will not preclude further testing of OS.

8.2 Sample size estimate

Approximately 530 patients will be randomized, globally, in a 1:1 ratio (AZD9291: SoC EGFR TKI) to this study. The primary endpoint of the study is PFS based on Investigator assessment (according to RECIST v1.1). Progression free survival analysis will be performed at approximately 29 months after FPI for 12 months recruitment (or 30 months for 15 months recruitment).

The primary analysis of PFS will occur when approximately 359 progression events have been observed in the 530 globally randomized patients. If the true PFS hazard ratio (HR) for the comparison of AZD9291 versus SoC EGFR TKI is 0.71, 359 progression events will provide 90% power to demonstrate a statistically significant difference in PFS at a 5% 2-sided significance level (translating to an approximate improvement in median PFS from 10 to

14.1 months assuming exponential data distribution and proportional hazards). The minimum critical HR is 0.81 (e.g. 10 to 12 months).

In order to randomise 530 patients, 980 EGFRm+ patients will need to be screened.

For the key secondary endpoint of PFS in patients with T790M+ using a highly sensitive assay, there will be approximately 72% power to detect a PFS HR=0.55 (e.g., 10 to 18 months), assuming a prevalence of 20%.

For the OS analysis, there will be approximately 72% power to demonstrate a HR <0.75 (i.e., 25 to 33.3 months) with 2-sided 5% significance level.

Once 530 patients have been recruited globally, recruitment will continue in mainland China only until approximately 120 patients have been recruited in China. This is being done to ensure adequate Chinese patient participation to satisfy China FDA requirements.

Sample size estimates have been calculated using EAST version 6.3.

8.3 Definitions of analysis sets

8.3.1 Full Analysis Set

The full analysis set (FAS) will include all randomised patients prior to the end of global recruitment. Any patients recruited in China, after global recruitment has ended, will not be included in the FAS (see Section 8.6). The full analysis set will be used for all efficacy analyses and treatment groups will be compared on the basis of randomised study treatment, regardless of the treatment actually received.

8.3.2 Safety Analysis Set

The safety analysis set (SAS) will consist of all patients recruited prior to the end of global recruitment who received at least one dose of study treatment and for whom post-dose data are available. Any patients recruited in China only, after global recruitment has ended, will not be included in the safety analysis set (see Section 8.6) Safety data will not be formally analysed but summarised using the safety analysis set, according to the treatment received; i.e., erroneously treated patients (e.g., those randomised to treatment A but actually given treatment B) will be summarised according to the treatment they actually received.

8.3.3 Pharmacokinetic Analysis Set

Pharmacokinetic Analysis Set is defined as patients in the FAS who have at least one measurable PK concentration, supported by the relevant date and time of this sample; and for each time a PK sample was taken, the dosing data for that day; and for samples taken after multiple dosing, the dosing data for the 2 days prior to the sample day as well as the sample day. For any individual sample to be included in the PK analysis set, the full sample data and dosing data need to be present for that sample.

The pharmacokinetics will agree to the strategy for dealing with data affected by protocol deviations before any formal statistical analysis is performed. Important protocol deviations include changes to the procedures that may impact the quality of the data or any circumstances that can alter the evaluation of the PK. Examples include, but not limited to, vomiting following oral dosing occurring within the timeframe of 2 times the median tmax; sample processing errors that lead to inaccurate bioanalytical results; incomplete dose administered; incomplete PK profile collected; and/or use of disallowed concomitant medication. In the case of an important protocol deviation or event, affected PK data collected will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings. Important deviations will be listed and summarised in the CSR.

8.3.4 Centrally confirmed EGFR Analysis Set

The centrally confirmed EGFR Analysis Set is defined as patients in the FAS who have centrally confirmed EGFRm+ with either Ex19del or L858R substitution mutations.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

Investigator RECIST-based assessments

From the investigators review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST v1.1.

At each visit, patients will be programmatically assigned a RECIST v1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) unless there is any evidence of progression in which case the response will be assigned as PD.

Please refer to Appendix C for the definitions of CR, PR, SD, and PD.

The investigator RECIST assessments will be used in the calculation of all RECIST-based endpoints (PFS, ORR, DoR, DCR, depth of response). The data from the BICR of RECIST assessments will be used as a sensitivity analysis.

Blinded Independent Central Review of RECIST based assessments

The BICR of radiological imaging data will be carried out using RECIST v1.1. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows) will be provided to the BICR. All imaging scans will be reviewed by 2 independent radiologists using RECIST v1.1 criteria and will be adjudicated if required. The independent reviewers will be blinded to treatment.

Tumour assessment will be performed using contrast enhanced CT or MRI of chest and abdomen (including liver and adrenal glands) and other regions as clinically indicated. Duplicate images will be collected for the BICR. For each patient, the BICR will define the

overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each time point (i.e., for visits where response or progression is not identified). If a patient has had a tumour assessment which cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is any evidence of progression in which case the response will be assigned as PD). Progression free survival will be derived from the overall visit response date and the scan dates.

Further details of the BICR will be documented in the Independent Review Charter.

Progression free survival

Progression-free survival is defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable visits or does not have baseline data, they will be censored at 0 days unless they die within 2 visits of baseline.

The PFS time will always be derived based on scan/assessment dates not visit dates.RECIST assessments/scans contributing towards a particular visit may be performed on different dates.

The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

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 up 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 was received will not be included in the numerator for the ORR calculation (where the FAS will be the denominator).

Duration of Response

Duration of Response will be defined as the time from the date of first documented response (i.e., subsequently confirmed) until the date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of

progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If the response is not confirmed, it will not be included.

If a patient does not progress following a response, then his/her duration of response will use the PFS censoring time.

Disease Control Rate

Disease Control Rate is defined as the percentage of patients who have a best overall response of CR or PR or SD.

Depth of response

Depth of response is defined as the relative change in the sum of the longest diameters of RECIST target lesions at the nadir in the absence of new lesions or progression of non-target lesions compared to baseline. The absolute change and percentage change from baseline in the sum of tumour size at each assessment will be calculated. The best change in tumour size will include all assessments prior to progression or start of subsequent anti-cancer therapy.

Overall survival

Overall survival is defined as the time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made in the 1 week following the date of the data cut-off for each OS analysis, and if subjects are confirmed to be alive, or if the death date is post the final data cut-off date, these subjects will be censored at the date of the final data cut off. Death dates may be found by checking publicly available death registries.

[redacted]
CCI
[redacted]

Time to first subsequent therapy or death

Time to first subsequent therapy (TFST) or death is defined as the time from the date of randomisation to the earlier of the date of anti-cancer therapy start date following study drug discontinuation or death. Any patient not known to have had a subsequent therapy or not known to have died at the time of the analysis will be censored at the last known time to have not received subsequent therapy; i.e., the last follow-up visit where this was confirmed.

Time to second subsequent therapy or death

Time to second subsequent therapy (TSST) or death is defined as the time from the date of randomisation to the earlier of the date of second subsequent anti-cancer therapy start date following study drug discontinuation or death. Any patient not known to have died at the time of the analysis and not known to have had a second subsequent therapy will be censored at the last known time to have not received second subsequent therapy, i.e., the last follow-up visit where this was confirmed.

Brain metastases

The number of patients developing brain metastasis during the study treatment will be summarised.

Health-related Quality of Life & symptoms

Patient Reported Outcomes will be assessed using the EORTC QLQ-C30, EORTC QLQ-LC13, CTSQ-16, and PRO-CTCAE questionnaires.

EORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC QLQ-C30 consists of 30 questions, which can be combined to produce 5 functional scales (Physical, Role, Cognitive, Emotional, Social), 3 symptom scales (Fatigue, Pain, Nausea/vomiting), 5 individual items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea), and a global measure of health status. The EORTC QLQ-LC13 is a lung cancer specific module comprising 13 questions to assess lung cancer symptoms (cough, haemoptysis, dyspnoea, and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia) and pain medication. With the exception of a multi-item scale for dyspnoea, all are single items.

An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/items, the functional scales and the global health status scale in the EORTC QLQ-C30, and for each of the symptom scales/items in the EORTC QLQ-LC13 according to the EORTC QLQ-C30 Scoring Manual and EORTC QLQ-LC13 instructions.

Higher scores on the global health status and functioning scales indicate better health status/function. Higher scores on the symptoms scales indicate greater symptom burden.

The primary PRO outcome measures will be patient-reported lung cancer symptoms assessed using the EORTC QLQ-LC13, namely:

- Dyspnoea (multi-item scale based on 3 questions: “Were you short of breath when you rested; walked; climbed stairs?”),
- Cough: 1 item (“How much did you cough?”),
- Haemoptysis: 1 item (“Did you cough up blood?”),

- Pain: 3 individual items ("Have you had pain in your chest; your arm or shoulder; other parts of your body?").

Please refer to Appendix E for details on the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires.

Definition of clinically meaningful changes

Changes in score compared to baseline will be evaluated. A minimum clinically meaningful change is defined as a change in the score from baseline of ≥5 for scales/items from the EORTC QLQ-LC13 and ≥10 for scales/items from the EORTC QLQ-C30 (Osoba et al 1998).

For example, a clinically meaningful deterioration or worsening in chest pain (as assessed by EORTC QLQ-LC13) is defined as an increase in the score from baseline of ≥5. A clinically meaningful improvement in fatigue (as assessed by EORTC QLQ-C30) is defined as a decrease in the score from baseline of ≥10.

At each post-baseline assessment, change in symptoms/functioning from baseline will be categorised as improved, stable, or worsening as shown in Table 8.

Table 8 Visit response for health-related quality of life and disease-related symptoms

Score	Change from baseline	Visit response
LC13 symptom scales/items	≥+5	Worsened
	≤-5	Improved
	Otherwise	Stable
C30 symptom scales/items	≥+10	Worsened
	≤-10	Improved
	Otherwise	Stable
C30 functional scales and Global health status	≥+10	Improved
	≤-10	Worsened
	Otherwise	Stable

C30 = core 30 items; LC13 = lung cancer 13 items.

Time to symptom deterioration

For each of the symptom scales/items in EORTC QLQ-LC13, EORTC QLQ-C30 (both symptom and functional scales) as well as Global Health Status. time to symptom deterioration will be defined as the time from randomisation until the date of first clinically meaningful symptom deterioration (defined from a change from baseline as detailed in Table 8) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms progress after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data, they will be censored at Day 1. The population for analysis of time to symptom deterioration will include a subset of the FAS population who have baseline scores ≤95.

Symptom Improvement Rate

The Symptom Improvement Rate will be defined as the number (%) of patients with 2 consecutive assessments at least 18 days apart (i.e., 21 days allowing a visit window of 3 days), which showed a clinically meaningful improvement (a decrease from baseline score ≥5 for EORTC QLQ-LC13 scales/items or >10 for EORTC QLQ-C30 scales/items) in that symptom from baseline. The denominator will consist of a subset of the FAS population who have a baseline symptom score ≥5 (EORTC QLQ-LC13 scales/items) or ≥10 (EORTC QLQ-C30scales/items).

Mixed models repeated measures (MMRM) of change from baseline in primary PRO symptoms

Change from baseline for the primary PRO items of Dyspnoea, Cough, and Pain in Chest located on EORTC QLQ-LC13, in addition to Fatigue and Appetite loss collected using EORTC QLQ-C30 will be analysed using an MMRM model.

The MMRM model will include patient, treatment, visit (generic) and treatment by visit interaction as explanatory variables, the baseline PRO score as a covariate along with the baseline PRO score by visit interaction. More detail of the MMRM approach can be found in the FLAURA study SAP.

Patient reporting of Cancer Therapy Satisfaction Questionnaire-16

The CTSQ-16 index comprises 16-items that assess satisfaction with and preference for chemo, hormonal, and biological therapies in either oral (pill) and/or IV form. Expectations of therapy, feelings about side-effects, and satisfaction with therapy will be assessed.

Please refer to Appendix E for details on the CTSQ-16 questionnaire scores.

Patient reporting of CTCAE symptoms

The PRO-CTCAE questionnaire will be used to derive patient reporting of CTCAE symptoms. The PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. Not all items are administered in this study. Only 17 items are considered relevant for this cancer treatment, i.e., rash, skin dryness, acne, itching, nail loss, nail ridging, nail discoloration, sensitivity to sunlight, decreased appetite, nausea, vomiting, diarrhoea, fecal incontinence, fatigue, blurred vision, mouth/throat sores, and nosebleeds.

Please refer to Appendix E for details on the PRO-CTCAE questionnaire scores.

Health Resource Use Module

The Health Resource Use Module will be assessed in terms of symptoms for admission and type of admission (planned/unplanned hospitalisation, outpatient visits, or emergency department visits).

8.4.2 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs (pulse and BP), ECG, LVEF, WHO performance status, and ophthalmologic assessment. These will be collected for all patients.

Adverse events

Adverse events (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient.

Any AE occurring before treatment with study drug will be included in the data listings but will not be included in the summary tables of AEs.

Any AE occurring within 28 days of discontinuation of study drug (i.e., the last dose of AZD9291/SoC EGFR-TKI) will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study drug) will be flagged in the data listings. Please refer to Section 6.3.1.

Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on

the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs (pulse and BP)/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

8.4.3 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the plasma concentration data for AZD9291 and its metabolites will be performed by or on behalf of Quantitative Clinical Pharmacology (QCP), Alderley Park, AstraZeneca.

Plasma concentrations will be listed and summarised by sampling interval in the CSR. The ratio of metabolite to AZD9291 will also be calculated and summarised.

Pharmacokinetic data from this study will be analysed using a population PK approach, which may include exploring the influence of covariates on PK, if the data allow. The data collected in this study may also be combined with similar data from other studies and explored using population PK and/or pharmacokinetic-pharmacodynamic methods. The results of any such analyses will be reported separately from the CSR.

8.5 Methods for statistical analyses

All efficacy analyses will be performed on the FAS population. Results of all statistical analyses will be presented using a 95% confidence interval (CI) and 2-sided p-value.

8.5.1 Analysis of the primary variable

Progression free survival per the Investigator assessment for patients in the FAS will be analysed using a log rank test stratified by race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R) for generation of the p-value and using the Breslow approach for handling ties. The HR and CI will be obtained directly from the U and V statistics as follows (Berry et al 1991; Robins et al 1991; Robins 1993; Selke & Siegmund 1983):

$$HR = exp\left(\frac{U}{V}\right)$$

$$95\%\ CI\ for\ HR = \left(exp\left\{\frac{U}{V} - \frac{1.96}{\sqrt{V}}\right\}, exp\left\{\frac{U}{V} + \frac{1.96}{\sqrt{V}}\right\}\right)$$

Where $U = \sum_k U_k = \sum_k \sum_i (d_{1ki} - e_{1ki})$ is the stratified log-rank test statistic (with d_{1ki} and e_{1ki}, the observed and expected events in group 1, stratum k) and $\sqrt{V} = \sqrt{\sum_k V_k}$ is the standard deviation of the log-rank test statistic obtained from the LIFETEST procedure with a STRATA term for the stratification variable.

The assumption of proportionality will be assessed. In the event on non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. Proportionality will be tested firstly by examining the plots of complementary log-log (event times) versus log (time) and, if necessary, a time dependent covariate will be fitted to assess the extent to which this represents random variation.

A Kaplan-Meier (KM) plot of PFS will be presented by treatment group.

The treatment effect HR and two-sided 95% CIs will also be presented on a forest plot, alongside subgroup analyses.

Sensitivity analyses

(a) Quantitative Interactions

The presence of quantitative interactions will be assessed by means of an overall global interaction test. This will be performed in the overall population by comparing the fit of a Cox proportional hazards model including treatment, all covariates, and all covariate-by-treatment interaction terms, with one that excludes the interaction terms and will be assessed at the 2-sided 10% significance level. If the fit of the model is not significantly improved, then it will be concluded that overall, the treatment effect is consistent across the subgroups.

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process, all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

Any quantitative interactions identified using this procedure will then be tested to rule out any qualitative interaction using the approach of Gail and Simon (Gail & Simon 1985).

(b) Ascertainment bias

The possibility of bias in assessment and measurement of PFS by Investigators will be assessed using the BICR assessment of disease progression by RECIST. The HR from Investigator assessment and BICR assessment of PFS will be assessed. If they are sufficiently close, no more scans will be reviewed. If they are not sufficiently close, all scans will be reviewed and a HR calculated from the BICR of all patients. The evaluation bias will be further assessed through the use of the early discrepancy rate and the late discrepancy rate. Further details will be provided in the SAP.

(c) Evaluation-time bias

In order to assess possible evaluation-time bias that could occur if scans are not performed at the protocol-scheduled time points, the midpoint between the time of progression and the previous evaluable RECIST assessment will be analysed using a log rank test stratified by race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R), as described for the primary analysis of PFS.

d) Attrition bias

Possible attrition bias will be assessed by repeating the primary PFS analysis, except that the actual PFS event times rather than the censored times of patients who progressed or died in the absence of progression immediately following 2 or more non-evaluable tumour assessments, will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. A Kaplan-Meier plot of the time to censoring, where the censoring indicator of the primary PFS analysis is reversed, will be presented.

Subgroup analysis

In addition to the analysis of PFS described above, the following subgroup analyses will be conducted by comparing PFS between treatments (i.e., using a Cox-Proportional Hazards Model) in the following groups:

- Gender (Male versus Female)
- Race (Asian/Non-Asian)
- Age at screening (<65 versus ≥65)
- CNS metastases at entry
- Smoking history
- EGFR mutation (Ex19del, L858R)
- EGFR by ctDNA (Positive, Negative, Missing)
- Centrally confirmed EGFR (Positive, Negative, Missing)
- WHO performance status (0, 1)

8.5.2 Analysis of the secondary variables

8.5.2.1 Hierarchical testing of key secondary variables

Since two analyses of OS are planned, the Lan DeMets approach that approximates the O'Brien and Fleming spending function will be used to maintain an overall 2-sided 5% type I error across the two planned analyses of OS.

The significance level for the OS analyses will be calculated using the statistical software packed EAST by specifying the information fraction for each analysis. The information fraction is calculated as the number of OS events at the interim analysis time-point divided by the total number of events at the final analysis time-point.

Any non-statistically significant OS analyses at the time of the primary analysis of PFS will not preclude further testing of OS.

No other formal statistical testing will be conducted on the study's other secondary endpoints.

8.5.2.2 Analysis of progression free survival subgroup

Progression free survival in patients by EGFR Ex19del or L858R substitution mutations (prospectively stratified) will be analysed using a Cox Proportional Hazards Model including treatment, race (Asian/Non-Asian), mutation type (Ex19del / L858R), and the treatment by mutation type interaction term. The results of the analysis will be presented in terms of a HR together with its associated 95% CI and 2-sided p-value for patients with Ex19del and separately for patients with L858R.

8.5.2.3 Analysis of overall survival

The analysis of OS in the globally recruited population will occur at 2 time points:

- At the time of the primary analysis of PFS.
- At approximately 60% maturity. For example; 60% maturity would be achieved when approximately 318 death events (across both arms) have occurred in the planned approximately 530 globally recruited patients. It is predicted that 318 death events will be observed at approximately 45 months from FPI for 12 months recruitment (47 months for 15 months recruitment). For the OS analysis, there will be approximately 72% power to demonstrate a HR<0.75 (i.e., 25 to 33.3 months) with 2-sided 5% significance level.

The separate analyses of OS in the cohort recruited in mainland China will also be conducted at 2 time points:

- At the time of the primary China cohort analysis of PFS, scheduled to occur at approximately the same PFS maturity as observed at the primary global PFS analysis.
- At approximately 60% OS maturity within the China-only cohort.

Overall survival data will be analysed using the same methodology and model as for the analysis of PFS provided there are sufficient events available for a meaningful analysis (>20 deaths [if not, descriptive summaries will be provided]).

Overall survival will also be analysed for the same pre-defined subgroups during the final 60% maturity OS analysis as in the PFS subgroup analyses conducted during the primary PFS

analysis. Each subgroup must have at least 20 OS events per subgroup level in order for that subgroup level to be included in the OS subgroup analysis.

Additional analysis of overall survival adjusting for the impact of patients randomized to SoC, who subsequently receive AZD9291 would be completed if this treatment sequence occurs in a significant proportion of patients. Methods such as Rank Preserving Structural Failure Time (RPSFT) (Robins et al 1991), Inverse Probability of Censoring Weighting (IPCW) (Robins 1993) and other methods in development may be explored. The decision to adjust and final choice of methods will be based on the plausibility of the underlying assumptions. Further detail will be provided in the SAP and Payer Analysis Plan

8.5.2.4 Analysis of Objective Response Rate

Objective Response rate will be analysed using a logistic regression stratified by race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood CI and 2-sided p-value.

8.5.2.5 Analysis of Duration of Response

In order to analyse the secondary outcome variable of DoR between arms, the Expected Duration of Response (EDoR) will be derived for each treatment arm (Ellis et al 2008). The EDoR is the product of the proportion of patients responding to treatment and the mean DoR in responding patients, and provides an estimate based on all randomised patients. Treatments will be compared by calculating the ratio of EDoRs using an appropriate probability distribution for duration of response in responding patients. The choice of probability distribution will be detailed in the SAP. The analysis of DoR will be stratified by the same covariates as the primary analysis, weighting each stratum inversely proportional to the within stratum variance of the log of the ratio of EDoRs. Additionally, descriptive data will be provided for the DoR in responding patients, including associated Kaplan-Meier curves (without any formal comparison or p-value attached).

8.5.2.6 Analysis of Disease Control Rate

Disease Control Rate will be analysed using a logistic regression. The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood CI and 2-sided p-value.

8.5.2.7 Analysis of depth of response

Depth of response (i.e., tumour shrinkage / change in tumour size) will be examined by summarizing the absolute change in target lesion tumour size from baseline, and percentage change in target lesion tumour size from baseline using descriptive statistics and presented at each time point and by randomised treatment group. The effect of AZD9291 on best percentage change in tumour size will be estimated from an analysis of covariance (ANCOVA) model. The number of patients, unadjusted mean, and least squares means for each treatment group will be presented, together with the difference in least squares means, 95% CI and corresponding p-value.

8.5.2.8 Analysis of time to Patient Reported Outcome symptom deterioration

Time to PRO symptom deterioration will be analysed using a log rank test stratified by race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R) for generation of the p-value and using the Breslow approach for handling ties. The HR and CI will be calculated using the same methodology as for the primary endpoint.

8.5.2.9 Analysis of Patient Reported Outcome Symptom Improvement Rate

Symptom Improvement Rate will be analysed using a logistic regression. The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood confidence interval and 2-sided p-value.

8.5.2.10 Analysis of CTSQ-16

The 3 domains of interest (Expectations with Therapy, Feelings about Side-Effects, and Satisfaction with Therapy) will be analysed as appropriate to compare for significant differences between treatment groups at each time point. Further details will be provided in the SAP.

8.5.2.11 Sensitivity analyses for centrally confirmed EGFRm+ patients

As sensitivity to the main analyses of PFS and other secondary endpoints, analyses of these endpoints will be performed using the centrally confirmed EGFR analysis set. Any discordance between local and central tests will be explored; full details will be given in the SAP.

8.5.2.12 Pharmacokinetics

Pharmacokinetics data from this study will be analysed using a population PK approach and may also form part of a pooled analysis with other AZD9291 studies; results from these analyses will be reported separately from the CSR.

Pharmacokinetic concentration data will be summarised using appropriate summary statistics, and further details will be provided in the SAP.

8.5.3 Exploratory analysis

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8.6 Post primary PFS – global cohort

All the previous text in section 8 was applicable up to the primary PFS. Any changes from the approved protocol as at DBL to the statistical analysis plans, testing hierarchy and/or methodology was documented in version 3 of the SAP which was also approved prior to the data cut off for the primary analysis.

8.6.1 Final OS analysis

A final OS analysis will be conducted at approximately 60% maturity. Overall survival data will be analysed using the same methodology and model as for the analysis of PFS. Subgroups may also be explored.

Overall survival will also be analysed for the same pre-defined subgroups during the final 60% maturity OS analysis as in the PFS subgroup analyses conducted during the primary PFS analysis. Each subgroup must have at least 20 OS events per subgroup level in order for that subgroup level to be included in the OS subgroup analysis.

Due to more than one OS analysis being conducted, an O-Brian and Fleming spending function will be applied to strongly control the type I error at 5% 2-sided. The remaining alpha will be assigned to this analysis. For example, if the information fraction at the interim analysis was 0.42, the 2 alpha levels required to declare statistical significance would be 0.0015 and 0.0495 at the interim and final analysis respectively when taking into account the

correlation. EAST software will be used to calculate the exact significance level based on the number of OS events.

Additional analysis of overall survival adjusting for the impact of patients randomized to SoC, who subsequently receive AZD9291 would be completed if this treatment sequence occurs in a significant proportion of patients. Methods such as Rank Preserving Structural Failure Time (RPSFT) (Robins et al 1991), Inverse Probability of Censoring Weighting (IPCW) (Robins 1993) and other methods in development may be explored. The decision to adjust and final choice of methods will be based on the plausibility of the underlying assumptions. Further detail will be provided in the SAP and Payer Analysis Plan.

8.6.2 Supporting summaries

In addition to the overall survival analysis, the following will be summarised:

- Primary cause of death
- Adverse events
- Concomitant medications and procedures
- Anti-cancer and surgery treatments

PRO and RECIST derived endpoints will not be summarised at the time of the final OS analysis. This includes PFS and PFS2. However, subsequent treatment and exposure data will continue to be collected, and TFST and TSST will be analysed and presented at the time of the final OS analysis.

Further detail will be provided in the SAP.

8.7 China cohort

The safety and efficacy data collected for the China cohort will be combined with data from the Chinese patients recruited prior to the end of global recruitment, and summarised, analysed and reported separately from the Clinical Study Report. Hence a patient randomised in China prior to the end of global recruitment will be included in both the (globally recruited) FAS and the China-only FAS. A patient randomised in China after the end of global recruitment will be included only in the China-only FAS.

These analyses will be performed when the PFS data from the China patients is of similar maturity to when the analysis of PFS for the globally recruited patients will be conducted; i.e. approximately 68% maturity or approximately 82 PFS events out of the approximately 120 China patients.

The China-only Full analysis set will include all patients randomised in China and will be used for all China-only efficacy analyses. This includes all patients randomised in China prior to the end of global recruitment and all additional patients recruited in mainland China after global recruitment is completed.

The China-only safety analysis set will consist of all patients recruited in China who received at least one dose of study treatment and for whom post-dose data are available.

All efficacy, safety, PRO and PK variables will be derived in the same way as detailed in Section 8.4.

All analyses detailed in Section 8.5 to address primary, secondary of safety objectives will be repeated for the patients randomised in China using the analysis sets described above. The primary statistical analysis of the efficacy of AZD9291 for China-only FAS patients will be an assessment of progression free survival based on investigator assessment.

All statistical analyses will be considered exploratory and only performed if sufficient numbers of events or patients are available (e.g. ≥20 PFS or OS events), otherwise descriptive statistics only will be presented. No adjustment for multiplicity will be made and so the procedure for hierarchical testing detailed in Section 8.5.2.1 will not be followed.

Statistical analyses will only include a stratification variable for mutation type (Ex19del versus L858R), and will not include race (Asian versus Non-Asian).

Updated safety summaries may also be produced which include safety data from all patients who received at least one dose of randomized treatment (AZD9291 or SoC) if requested by health authorities.

Further details will be provided in the SAP.

8.8 Post China primary PFS – China cohort

All the previous text in section 8.7was applicable up to the china primary PFS. Any changes from the approved protocol as at DBL to the statistical analysis plans and/or methodology was documented in version 3 of the SAP which was also approved prior to the data cut off for the primary analysis.

8.8.1 Final OS

A final OS analyses will be performed when the OS data from the China patients is of similar maturity to when the final analysis of OS for the globally recruited patients will be conducted; i.e. approximately 60% maturity or approximately 82 OS events out of the approximately 120 China patients. This will be analysed separately to the final OS for globally recruited patients, regardless of timing.

8.8.2 Supporting summaries

In addition to the overall survival analysis, the following will be summarised:

- Primary cause of death
- Adverse events
- Concomitant medications and procedures
- Anti-cancer and surgery treatments

PRO and RECIST derived endpoints will not be summarised at the time of the final OS analysis. This includes PFS and PFS2. However, subsequent treatment and exposure data will be collected, and TFST, and TSST will be analysed and presented at the time of the final OS analysis.

Further detail will be provided in the SAP.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA (OR DELEGATE)

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and the EDC and ePRO systems 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 eCRFs, 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 eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts).

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the site should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

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

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

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

The study is expected to start in Quarter 4 2014 and to end by Quarter 2 2019.

The study may be terminated at individual study sites 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 PAREXEL, according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the AstraZeneca

Drug Dictionary. Classification coding will be performed by the Medical Coding Team at PAREXEL.

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.

Serious adverse event reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data management of genotype data

Any genotype data generated in this study will be stored in the AstraZeneca genotyping Laboratory Information Management System (LIMS) database, or other appropriate secure System within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the eCSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

Management of external data

Data associated with ePRO will be transferred from the vendor to Parexel.

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/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

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

Details of patient data protection are detailed in Appendix F.

10.3 Ethics and regulatory review

An Ethics Committee (EC)/IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

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

Each Principal Investigator is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each study site will:

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

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International Coordinating Investigators and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol. The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca will distribute any new versions of the Clinical Study Protocol to each Principal Investigator(s). For distribution to EC/IRB see Section 10.3.

If a change to a Clinical Study Protocol requires a change to a site's ICF, AstraZeneca and the site's EC/IRB are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC/IRB.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC/IRB may perform audits or inspections at the study site, 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, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the study site.

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Appendix A Signatures (Not Applicable)

Appendix B Guidance Regarding Potential Interactions with Concomitant Medications

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

B1 DRUGS INDUCING CYP3A4 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMEND ARE NOT COMBINED WITH AZD9291

AZD9291 is metabolised by CYP3A4 and CYP3A5 enzymes.

A drug-drug interaction study of AZD9291 evaluated in patients showed that there is potential for AZD9291 being a victim when co-administered with strong inducers of CYP3A4 (AZD9291 concentrations are decreased when co-dosed with rifampicin).

The following potent inducers of CYP3A4 must not be used during this study for any patient receiving AZD9291.

Table 9 Drugs inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to AZD9291 start
Carbamazepine, phenobarbital, phenytoin Rifampicin, rifabutin, rifapentine St John's Wort	3 weeks
Phenobarbitone	5 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

B2 MEDICINES WHOSE EXPOSURES MAY BE AFFECTED BY AZD9291 THAT ASTRAZENECA CONSIDERS MAY BE ALLOWED WITH CAUTION

AZD9291 may increase the concentration of sensitive BCRP substrates (concentration of the sensitive BCRP substrate, rosuvastatin, is increased).

Table 10 Exposure, pharmacological action and toxicity may be increased or decreased by AZD9291

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine Doxorubicin Daunorubicin Topotecan	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD9291.

B3 DRUGS THAT PROLONG QT INTERVAL

The drugs listed in this section are taken from information provided by the Arizona Center for Education and Research on Therapeutics website: https://crediblemeds.org/. The website categorises drugs based on the risk of inducing Torsades de Pointes (TdP).

During screening the drugs that patients are currently prescribed should be checked opposite the ArizonaCert website.

Drugs with a known risk of TdP must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table 11 Drugs with a known risk of TdP and should not be administered during treatment and for a period of two weeks after discontinuing study treatment. The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such investigators are recommended to search the website to provide the most up to date information.

Table 11 Drugs with a known risk of TdP

Drug name	Withdrawal period prior to study treatment start
Anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine terlipressin	2 days
Cilostazol, Cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days
Azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide* Ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, Probucol, vandetanib	4 months
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

Patients receiving drugs from other TdP risk categories can be enrolled, notwithstanding other exclusions and restrictions, if these drugs are considered essential for patient management. Drug exposure should have reached steady state (≥5 half-lives) prior to study treatment initiation.

Following study treatment initiation if it is considered essential for patient management to give drugs known to prolong QTc interval, regardless of TdP risk category, close monitoring with ECGs and electrolytes is recommended.

Appendix C Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

C1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D5160C00007 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

C2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated and not chosen for biopsy during the screening period.

Measurable:

A lesion, not previously irradiated and not chosen for biopsy during the screening period, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. If only one measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions**
- Skin lesions assessed by clinical examination
- Brain metastasis
- Lesions biopsied within the screening period (exception: If only one measurable lesion exists, it is acceptable to be used [as a target lesion] as long as it has not been previously

irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed).

* Nodes with <10mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

Special Cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

Non-Target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

C3. METHOD OF ASSESSMENT

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table 12 Summary of Methods of Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest x-ray	X-ray, Chest x-ray
		Ultrasound
		Bone Scan
		FDG-PET

CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D5160C00007 study it is recommended that CT examinations of the Chest and abdomen (including liver and adrenal glands), will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method although CT is acceptable.

Clinical examination

In the D5160C00007 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

X-ray

Chest X-ray

In the D5160C00007 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray

In the D5160C00007 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound

In the D5160C00007 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

In the D5160C00007 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

Tumour markers

In the D5160C00007 study tumour markers will not be used for tumour response assessments as per RECI ST 1.1.

Cytology and histology

In the D5160C00007 study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of

clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D5160C00007 study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

FDG-PET scan

In the D5160C00007 study FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

C4. TUMOUR RESPONSE EVALUATION

Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment (refer to Study Plan and section 5.1 from the study protocol). Follow-up assessments will be performed every 6 weeks (± 1 week) after randomisation until objective disease progression as defined by RECIST 1.1 even if a patient

discontinues treatment prior to progression or receives other anti-cancer treatment. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Target lesions (TL)Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

Table 13 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

Non-Target lesions (NTL)

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 14 Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans

confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 4.

Table 15 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NE	Non PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no NTLs at baseline).

C5. CENTRAL REVIEW

The Contract Research Organisation (CRO) appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

C6. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45 (2009) 228-247.

Appendix D Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

D1. INTRODUCTION

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

D2 DEFINITIONS

Potential Hy's Law (PHL)

A Potential Hy's Law (PHL) case is defined as a study patient with an increase in serum Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN irrespective of serum Alkaline Phosphatase (ALP), at any point during the study following the start of study medication.

Hy's Law (HL)

An HL case is defined as a study patient with an increase in serum AST or ALT ≥ 3x ULN together with TBL ≥ 2xULN, where no other reason can be found to explain the combination of increases, e.g., elevated serum ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL to be met the elevation in transaminases must precede or be coincident with (.i.e., on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

D3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will, without delay, review each new laboratory report and if the identification criteria are met, will:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

D4. FOLLOW-UP

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria, the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (See Section 6).
- Notify the AstraZeneca representative who will then inform the central Study Team.

The Study Physician contacts the Investigator to provide guidance, discuss, and agree on an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact, the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.

- Complete the three Liver eCRF Modules as information becomes available.

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

D5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.

- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.

  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made.

- Report an SAE (report term 'Potential Hy's Law') by applying serious criteria and causality assessment as per above.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

D6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients who meet PHL criteria on study treatment (including the 30 day follow-up period post discontinuation of study treatment) after having previously met PHL criteria at a study visit prior to starting study treatment.

At the first 'on-study treatment' occurrence of PHL criteria being met, the Investigator will:

Determine if there has been a significant change in the patient's condition compared with the last visit where PHL criteria were met:

- If there is no significant change, no action is required.

- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section 4.2 of this Appendix.

A 'significant' change in the patient's condition refers to a subsequent clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, and/or eosinophilia. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

D7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment (including the 30-day follow-up period) and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease or did the patient meet PHL criteria prior to starting study treatment and at their first 'on-study treatment' visit as described in Section 6?

If No: Follow the process described in Section 6 of this Appendix.

If Yes: Determine if there has been a significant change in the patient's condition compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in Section 4.2 of this Appendix.

A 'significant' change in the patient's condition refers to a subsequent clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms, such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, and/or eosinophilia. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

D8. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov

Appendix E Patient Reported Outcomes

CCI

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): __ __ __ __ __ __
Today's date (Day, Month, Year): 31 __ __ __ __ __ __

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1 2	3		4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1 2	3		4
27. Has your physical condition or medical treatment interfered with your social activities?	1 2	3		4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

CCI

CCI

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Cancer Therapy Satisfaction Questionnaire

US English

- The following pages ask some questions about your cancer therapy (IV/pills). Within this questionnaire, "Cancer therapy (IV/pills)" refers to your current or most recent cancer therapy or cancer pills (including: hormonal therapy, IV therapy, and cancer pills).

- Please read each question and answer as honestly as you can without the help of anyone.

- There are no right or wrong answers; the answers should be based on your own personal experiences.

- This questionnaire will take about 10 minutes to complete.

Your Thoughts about Cancer Therapy (IV/pills)

The following statements ask you to share your **thoughts about cancer therapy (IV/pills)**. Please answer each question below by *checking the box* that best represents your opinion (check only one box per question).

In general, in the last four weeks, how *often did you feel*:		**Always**	**Most of the time**	**Some-times**	**Rarely**	**Never**
1.	That cancer therapy (IV/pills) would help you to return back to a normal life?	☐5	☐4	☐3	☐2	☐1
2.	That cancer therapy (IV/pills) would get rid of the cancer?	☐5	☐4	☐3	☐2	☐1
3.	That cancer therapy (IV/pills) would help prevent the cancer from coming back?	☐5	☐4	☐3	☐2	☐1
4.	That cancer therapy (IV/pills) would stop the cancer from spreading?	☐5	☐4	☐3	☐2	☐1
5.	That your cancer therapy (IV/pills) limited your daily activities?	☐5	☐4	☐3	☐2	☐1
6.	Upset about the side effects?	☐5	☐4	☐3	☐2	☐1
7.	That cancer therapy (IV/pills) was worth taking even with the side effects?	☐5	☐4	☐3	☐2	☐1
8.	That cancer therapy (IV/pills) would help you live longer?	☐5	☐4	☐3	☐2	☐1

9. In general, **in the last four weeks**, how often did you think about stopping your cancer therapy (IV/pills)?

☐5	☐4	☐3	☐2	☐1
Always	Most of the time	Sometimes	Rarely	Never

Satisfaction with Cancer Therapy (IV/pills)

The following statements are about your satisfaction with your **most recent cancer therapy (IV/pills)**. Please answer each question below by *checking the box* that best describes your level of satisfaction (check only one box per question).

10. **Overall**, how worthwhile was your cancer therapy (IV/pills)?

☐6	☐4	☐3	☐2	☐1
Very worthwhile	Quite worthwhile	Moderately worthwhile	A little worthwhile	Not worthwhile at all

11. **Overall,** was taking cancer therapy (IV/pills) as difficult as you expected?

☐5	☐4	☐3	☐2	☐1
Much more difficult than I thought it would be	Somewhat more difficult than I thought it would be	As difficult as I thought it would be	Somewhat easier than I thought it would be	Much easier than I thought it would be

12. **Overall,** how well did the **benefits** of cancer therapy (IV/pills) meet your expectations?

☐6	☐4	☐3	☐2	☐1
Much better than my expectations	Somewhat better than my expectations	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

13. **Overall,** were the **side effects** of cancer therapy (IV/pills) as you expected?

☐5	☐4	☐3	☐2	☐1
Much better than I expected	Somewhat better than I expected	Exactly as I expected	Somewhat worse than I expected	Much worse than I expected

14. How satisfied were you with the **form** of your cancer therapy (IV/pills)?

☐5	☐4	☐3	☐2	☐1
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

15. **Overall,** how satisfied were you with your most recent cancer therapy (IV/pills)?

☐5	☐4	☐3	☐2	☐1
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

16. Taking everything into consideration, if given the choice again, would you decide to take this cancer therapy treatment?

☐5	☐4	☐3	☐2	☐1
Yes, definitely	Probably Yes	I don't know	Probably not	Definitely not

Thank you for your help.

English Version of selected PRO-CTCAE items:

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days…

RASH	
Did you have any RASH?	
O Yes	O No

DRY SKIN				
What was the SEVERITY of your DRY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

ACNE OR PIMPLES ON THE FACE OR CHEST				
What was the SEVERITY of your ACNE OR PIMPLES ON THE FACE OR CHEST at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

ITCHY SKIN				
What was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

FINGERNAILS OR TOENAILS	
Did you lose any FINGERNAILS OR TOENAILS?	
O Yes	O No

RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS	
Did you have any RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS?	
O Yes	O No

CHANGE IN COLOR OF YOUR FINGERNAILS OR TOENAILS	
Did you have any CHANGE IN COLOR OF YOUR FINGERNAILS OR TOENAILS?	
O Yes	O No

DECREASED APPETITE				
What was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

NAUSEA				
How OFTEN do you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

VOMITING				
How OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

LOOSE OR WATERY STOOLS (DIARRHEA)				
How OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

LOSE CONTROL OF BOWEL MOVEMENTS				
How OFTEN did you LOSE CONTROL OF BOWEL MOVEMENTS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
How much did LOSS OF CONTROL OF BOWEL MOVEMENTS INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

FATIGUE, TIREDNESS OR LACK OF ENERGY				
What was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

BLURRY VISION				
What was the SEVERITY of your BLURRY VISION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did BLURRY VISION INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

MOUTH AND THROAT SORES				
What was the SEVERITY of your MOUTH AND THROAT SORES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did MOUTH AND THROAT SORES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

INCREASED SKIN SENSITIVITY TO SUNLIGHT	
Did you have any INCREASED SKIN SENSIVITY TO SUNLIGHT?	
O Yes	O No

NOSEBLEEDS				
How OFTEN did you have NOSEBLEEDS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your NOSEBLEEDS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

Appendix F Pharmacogenetics Research

F1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the AZD9291 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD9291. Collection of deoxyribonucleic acid (DNA) samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD9291 but also susceptibility to the response/Non-small Cell Lung Cancer (NSCLC) for which AZD9291 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

F2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research CCI [redacted]

F3. GENETIC RESEARCH PLAN AND PROCEDURES

Selection of genetic research population

Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol, Section 3.1.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main body of the Clinical Study Protocol, Section 3.2.

Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main

study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.10 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at Visit 1 or after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 1, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 5.2.1.1 of the Clinical Study Protocol.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood or tumour tissue sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

F4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the main Clinical Study Protocol.

Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

F5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the Clinical Study Report (CSR) for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

F6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

F7. LIST OF REFERENCES

Not applicable.

Appendix G International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix H Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation.
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix I Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods

Definition of Women of Childbearing Potential

Women of Childbearing Potential (WoCBP):

Women between menarche and menopause who have not been permanently or surgically sterilised and are capable of procreation.

Women NOT of Childbearing Potential:

Women who are permanently or surgically sterilised or post-menopausal (definitions below):

Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).

- Women who have undergone tubal occlusion should be managed on trials as if they are of WoCBP (e.g. undergo pregnancy testing etc, as required by the study protocol).
- Women will be considered post-menopausal if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
- Women under 50 years old will be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range.
- Women over 50 years of age will be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments.

Acceptable contraception methods

Highly effective method of birth control is defined in Note 3 in ICH Guidance M3 (Nonclinical Safety Studies for the conduct of Human Clinical trials for Pharmaceuticals) as one that results in a low failure rate (e.g. less than 1 percent per year) when used consistently and correctly.

Note that women should have been stable on their chosen method of birth control for a minimum of 2 weeks before entering the trial. Generic names and examples of trade names are given. As trade names may vary, investigators should check the generic name of any contraception to ensure suitability.

Acceptable contraception methods are:

- Total sexual abstinence (abstinence must be for the total duration of the trial and the follow-up period)
- Vasectomised sexual partner plus male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
- Tubal occlusion plus male condom
- Intra-uterine Device (IUD) - provided coils are copper-banded, plus male condom
- Intra-uterine system (IUS) Levonorgestrel Intra Uterine System (eg, Mirena), plus male condom
- Medroxyprogesterone injections (Depo-Provera) plus male condom
- Etonogestrel implants (eg, Implanon, Norplan) plus male condom
- Normal and low dose combined oral contraceptive pills, plus male condom
- Norelgestromin / ethinylestradiol transdermal system plus male condom
- Intravaginal device (eg ethinylestradiol and etonogestrel) plus male condom
- Cerazette (desogestrel) plus male condom. Cerazette is currently the only highly efficacious progesterone based pill

Unacceptable contraception methods

The following methods are considered not to be highly effective and are therefore not acceptable contraceptive methods in AstraZeneca clinical trials:

- Triphasic combined oral contraceptives (COCs)
- All progesterone only pills except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing Intra-Uterine Devices (IUDs)
- Fertility awareness methods
- Coitus interruptus