Revised Clinical Study Protocol

Drug Substance	AZD9291
Study Code	D5160C00007
Edition Number	3.0

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, **Sweden**

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AstraZeneca Research and Development site representative

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Date

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1			
2			

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1			

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 Investigators:

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 enroled	Q4 2014	III
Estimated date of last patient completed globally	Q2 2018	

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 sensitising 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.

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. 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.

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.

The collection of data will stop at the time of the final OS analysis (note data will continue to be collected in patients recruited in mainland China until the final Chinese analysis if this is later). At this point the database will be closed and only SAEs 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 :**
To compare health resource use associated with AZD9291 treatment with SoC EGFR-TKI.	Health Resource Use Module
To assess AEs of AZD9291 compared with SoC EGFR-TKI therapy by patient self-reporting of specific CTCAE symptoms.	Patient Reported Outcome version of the CTCAE approximately 17 items (PRO-CTCAE) symptoms in countries where language is available.
To further assess the efficacy of AZD9291 compared to SoC EGFR-TKI post progression.	- Second progression free survival (PFS2). - Time to subsequent treatments.
To further characterise AZD9291 effects on survival.	- Impact of baseline potentially prognostic variables (e.g., tumour stage, performance status, sex, baseline lactate dehydrogenase [LDH]). - Time from enrolment to PFS2, time to subsequent treatments, and change in symptoms.
To explore the relationship between PK and selected endpoints (which may include efficacy, safety, and/or PRO), where deemed appropriate.	Correlation of PK with other primary/secondary/exploratory endpoints in patients treated with AZD9291.

To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence PK or response to AZD9291, SoC EGFR-TKI (gefitinib or erlotinib) (i.e., absorption, distribution, metabolism, excretion, safety, and efficacy) and/or susceptibility to/development of cancers.	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety or response observed in patients treated with AZD9291 or comparator.
To collect and store tumour and plasma samples for potential exploratory research into factors that may influence susceptibility to development of NSCLC and/or response to AZD9291 (where response is defined broadly to include efficacy, tolerability or safety) and to assess the relationship between blood-borne biomarkers and selected efficacy endpoints. Tissue and plasma samples may be used to support diagnostic development.	- Key genetic and proteomic markers to include, but not limited to, EGFR mutations, human epidermal growth factor receptor 2 (HER2), and proto-oncogene encoding Hepatocyte Growth Factor Receptor (cMET) expression and/or amplification. - Relationship between PK and blood-borne biomarkers. - Diagnostic development.
To explore the relationship between emergence of T790M in ctDNA derived from longitudinal plasma samples and time to progression for patients in the SoC EGFR-TKI.	Relationship between T790M in ctDNA and time to progression in SoC EGFR-TKI patients.
To compare the baseline tumour EGFR mutation status in all screened patients with evaluable results from baseline plasma samples.	Comparison of EGFR mutation status between tumour deoxyribonucleic acid (DNA) and plasma-derived ctDNA.
To compare plasma-derived ctDNA EGFR mutation status at baseline and at progression.	Comparison of EGFR mutation status in plasma samples at baseline and at progression.
To compare the tumour sample EGFR mutation status at baseline and from an optional tumour sample taken at progression.	Comparison of EGFR mutation status between tumour samples at baseline and at progression.

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 8.6).

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. 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.

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 Chinese patients recruited prior to the end of global recruitment, and summarised and analysed separately. 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
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 Organisation
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
DoR	Duration of Response

Abbreviation or special term	Explanation
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
HR	Hazard ratio
HRCT	High-resolution computed tomography

Abbreviation or special term	Explanation
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	Exon 21
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, Labor and Welfare
MRI	Magnetic resonance imaging
MUGA	Multi Gated Acquisition Scan
NCA	Non-compartmental analysis

Abbreviation or special term	Explanation
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
PAS	Pharmacokinetic Analysis Set
PD	Progression of disease
PFS	Progression free survival
PFS2	Time from randomisation 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
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
SAS	Safety Analysis Set
SD	Stable disease
SoC	Standard of Care
SPC	Summary of Product Characteristics

Abbreviation or special term	Explanation
SWT	Satisfaction with Therapy
T790M	An amino acid substitution at position 790 in EGFR, from a threonine to a methionine
T790M+	T790M mutation positive
TFST	Time to first 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
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 230 patients 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 (30 patients at 80 mg and 24 patients 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 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. 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 530 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 favorable 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).

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

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:

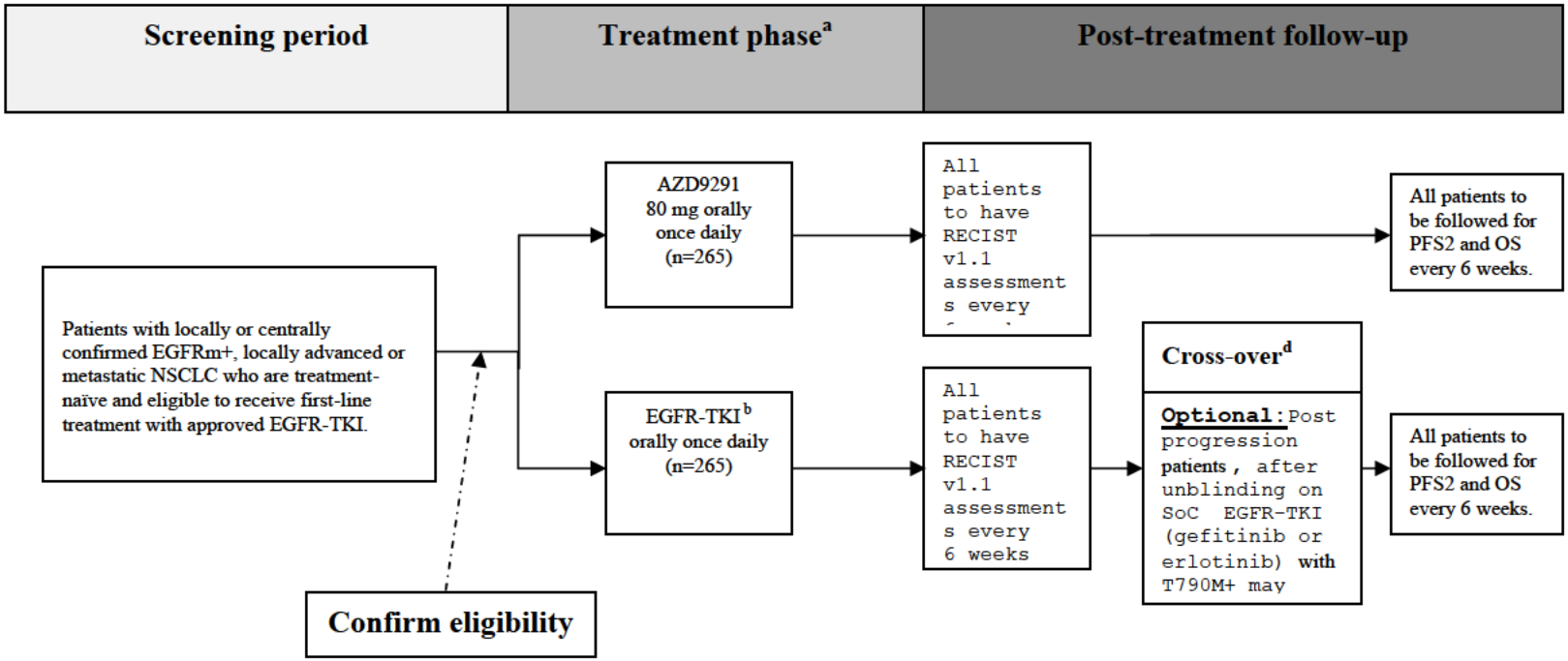
- Disease progression confirmed by independent central imaging review which must be established prior to a patient being unblinded. (Note: if central confirmation of progression is not confirmed, the patient is not eligible to receive open-label AZD9291 at that time. Should it be in the patients best 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 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. For further details on post-progression cross-over to AZD9291 please refer to Section 4.3.5.

Figure 1 Study flow chart



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 until objective 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 :**
To compare health resource use associated with AZD9291 treatment with SoC EGFR-TKI.	Health Resource Use Module
To assess AEs of AZD9291 compared with SoC EGFR-TKI therapy by patient self-reporting of specific CTCAE symptoms.	Patient Reported Outcome version of the CTCAE approximately 17 items (PRO-CTCAE) symptoms in countries where language is available.

To further assess the efficacy of AZD9291 compared to SoC EGFR-TKI post progression.	- Second progression free survival (PFS2). - Time to subsequent treatments.
To further characterise AZD9291 effects on survival.	- Impact of baseline potentially prognostic variables (e.g., tumour stage, performance status, sex, baseline lactate dehydrogenase [LDH]). - Time from enrolment to PFS2, time to subsequent treatments, and change in symptoms.
To explore the relationship between PK and selected endpoints (which may include efficacy, safety, and/or PRO), where deemed appropriate.	Correlation of PK with other primary/secondary/exploratory endpoints in patients treated with AZD9291.
To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence PK or response to AZD9291, SoC EGFR-TKI (gefitinib or erlotinib) (i.e., absorption, distribution, metabolism, excretion, safety, and efficacy) and/or susceptibility to/development of cancers.	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety or response observed in patients treated with AZD9291 or comparator.
To collect and store tumour and plasma samples for potential exploratory research into factors that may influence susceptibility to development of NSCLC and/or response to AZD9291 (where response is defined broadly to include efficacy, tolerability or safety) and to assess the relationship between blood-borne biomarkers and selected efficacy endpoints. Tissue and plasma samples may be used to support diagnostic development.	- Key genetic and proteomic markers to include, but not limited to, EGFR mutations, human epidermal growth factor receptor 2 (HER2), and proto-oncogene encoding Hepatocyte Growth Factor Receptor (cMET) expression and/or amplification. - Relationship between PK and blood-borne biomarkers. - Diagnostic development.
To explore the relationship between emergence of T790M in ctDNA derived from longitudinal plasma samples and time to progression for patients in the SoC EGFR-TKI.	Relationship between T790M in ctDNA and time to progression in SoC EGFR-TKI patients.

To compare the baseline tumour EGFR mutation status in all screened patients with evaluable results from baseline plasma.	Comparison of EGFR mutation status between tumour deoxyribonucleic acid (DNA) and plasma derived ctDNA.
To compare plasma-derived ctDNA EGFR mutation status at baseline and at progression.	Comparison of EGFR mutation status in plasma samples at baseline and at progression.
To compare the tumour sample EGFR mutation status at baseline and from an optional tumour sample taken at progression.	Comparison of EGFR mutation status between tumour samples at baseline and at progression.

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 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. In addition, the following are considered criteria for exclusion from the exploratory genetic research:
    - Prior allogeneic bone marrow transplant.
    - Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

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

1. 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.

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

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

Note: Section 3 describes the procedures to be carried out during Screening period.

3.4 Procedures for handling incorrectly enroled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enroled 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 authorisation prior to the site initiation.

Patients will be stratified at randomisation 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.

For Japan: Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigators or pharmacists, and the personnel who are independent to the study evaluation at the Patient Safety Department, AstraZeneca.

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.

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 reliable methods of contraception from the time of screening until 3 months after discontinuing study drug. Acceptable methods of contraception include total sexual abstinence, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions (Intra-uterine System [IUS] Levonorgestrel Intra Uterine System [Mirena], medroxyprogesterone injections [Depo-Provera]), copper-banded intra-uterine devices, and vasectomised partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse.

2. Male patients should be asked to use barrier contraceptives (i.e., by use of condoms) during sex with all partners during the trial and for a washout period of 3 months. Patients should avoid procreation for 6 months after completion of study drug treatment. Patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing study drug. If male patients wish to father children, they should be advised to arrange for freezing of sperm samples prior to the start of study drug.

3. Once enroled, 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 as well the use of medications known to prolong QTc interval; but patients may receive any medication that is clinically indicated for treatment of AEs. 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).

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 CYP3A4, or 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. Additionally, due to the potential CYP450 and p-glycoprotein induction risk exposure of drugs that are metabolized by CYP3A4, CYP1A2, or CYP2C or whose deposition disposition is mediated by p-glycoprotein could also be reduced and should also be monitored for potential reduction in therapeutic activity (especially those which have a narrow therapeutic index). Guidance on medications to avoid, medications that require close monitoring, and on washout periods should be provided (See Appendix B).

5. Up to 3-fold increase in statin exposure may occur when statins are coadministered with AZD9291. It is recommended that the starting and maintenance dose of statins should be as low as possible and should be guided by the statin label. Monitoring of low-density lipoprotein cholesterol (LDL-C) levels is advised. 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, the statin should be stopped, creatine kinase (CK) levels should be checked, and any appropriate further management should be taken.

6. Patients taking warfarin should be monitored regularly for changes in prothrombin time or International Normalized Ratio (INR).

7. Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE grade $\leq$2) while receiving treatment with AZD9291 until at least 1 week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade $\geq$3) ocular events, they must discontinue wearing their contact lenses until at least 1 week after treatment with AZD9291 is

permanently discontinued. Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by the Investigator, at any time during the study until 1 week after AZD9291 has been permanently discontinued. Patient should consult the site promptly if they have any concerns.

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 corneal ulceration or ILD will not be permitted to restart study treatment.

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.

For Japan: A patient that discontinues will always be asked about the reason(s) for discontinuation and the presence of any AEs. The Principal Investigator will perform the best possible observation(s), test(s), and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up (See Section 6.3.2); all unused study medications should be returned by the patient or representative.

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. Serious adverse events must be captured until the patient no longer has protocolled RECIST v1.1 assessments.

Note: Some assessments such as ePROs and further anti-cancer treatment should continue beyond first objective progression (according to RECIST v1.1) throughout the survival assessment period (See Table 1).

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

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												3, 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

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				Physical examination,
Height	X												Physical examination, height, and weight

Table 1 Study plan

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
WHO performance status	X	X			X	X	X	X then every 6w	X		X At start of subsequent treatment		WHO Performance Status
Pregnancy test (pre-menopausal female patients only)	X												Laboratory safety assessments
Ophthalmologic assessment	X	← as clinically indicated →											Ophthalmologic exam

Table 1 Study plan

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
Vital signs[e]	X	X	X	X	X	X	X	X then every 6w	X				Vital signs
Clinical chemistry/ Haematology/ Urinalysis[e]	X	X	X	X	X	X	X	X then every 6w	X				Laboratory safety assessments
Digital ECG[f]	X	X	X	X	X	X	X	X then every 6w	X				Electrocardiogram

Table 1 Study plan

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
Echocardiogram/MUGA (for LVEF)	X	every 12 weeks relative to first dose and as clinically required							X				Echocardiogram/multigated analysis scan
PK blood sample (including metabolites)[g]		X				X	X	X[g] every other cycle					5.4
Tumour samples upon disease progression (optional)									X (op)				5.7.2

Table 1 Study plan

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
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											RECIST v1.1

Table 1 Study plan

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]	EORTC QLQ-C30 and EORTC QLQ-LC13
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]	EORTC QLQ-C30 and EORTC QLQ-LC13

Table 1 Study plan

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

Table 1 Study plan

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
CTSQ-16[k]					X	X[m]							Cancer Therapy Satisfaction Questionnaire-16 items (CTSQ-16)
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]	Health Resource Use Module

Table 1 Study plan

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
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

Table 1 Study plan

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	Anti-cancer and surgical treatments
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.

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

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 development	X[b]								X[b]		5.7.3
Tumour assessments	X	← as per local practice →									
Subsequent response/ progression data		← every 6 weeks relative to randomisation →									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

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

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[g]		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 2 weeks following the date of the data cut-off for each OS analysis.]

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 **Error! Reference source not found.**). 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 tumour sample collection after progression, use of tumour and plasma samples for exploratory analysis, 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

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 **Error! Reference source not found.**).

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 Section 4.3.5 and Table 2, respectively.

4.3 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 and Table 2 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 as detailed in the Study Plan (See Table 1).

- 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

4.3.4 Survival follow-up

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. In addition to the survival status, the following assessments are also required post progression as detailed in the study plan (See Table 1):

- EORTC QLQ-C30 and Health Resource Use Module every 6 weeks until PFS2.
- EORTC QLQ-LC13 and PRO-CTCAE every 3 weeks until PFS2.
- Anti-cancer therapy and surgery collected every 6 weeks.
- Subsequent response/progression data every 6 weeks until the first confirmed disease progression on a subsequent treatment.

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.

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 data cut-off date for the primary PFS analysis, the central confirmation of disease progression will no longer be required (except for patients in China). For patients in China, after data cut-off date of China PFS analysis, the central confirmation of disease progression will be no longer 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 T790 M 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 Section7.1

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 Japan: The Principal Investigator/Investigator will record data on the observations, tests, and assessments specified in the protocol on the eCRFs provided by AstraZeneca. The eCRF will be accompanied with 'Instructions for the Investigator,' which should be followed. These instructions provide guidance for the recording of study data in the eCRF including how to change data incorrectly recorded.

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

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 perform the subsequent scans at their scheduled time points. 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 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

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 3 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 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.

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 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. Since confirmation by central imaging review is required for patients to cross-over to AZD9291, no patients will be permitted to cross-over without the aforementioned confirmation.

After data cut-off for the primary analysis of PFS in the patients randomised prior to the end of global recruitment has been completed, no further central collection of scans to assess response by RECIST is required except for sites in China. Any patients in China (either recruited prior to the end of the global recruitment or as part of the additional China cohort) should continue with central collection of scans to assess response by RECIST for independent assessment until the cut-off date of China PFS analysis.

5.1.3 Assessment of second progression

Following first objective progression, patients will have their progression status recorded every 6 weeks to assess time to second progression (PFS2). 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.

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).

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 3):

Table 3 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 4).

Table 4 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), 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), 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.

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.

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) and Table 2. 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.

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) 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.

Patients experiencing corneal ulceration will not be permitted to restart study drug.

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) 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. 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) for the timing of collection. 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.

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 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 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

Tumour and blood samples will be collected (as described in the Study Plan) and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, and clinical outcomes.

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 exploratory biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future studies.

5.7.1 Provision of additional tumour material for exploratory research

In addition to mandatory provision of tumour material at baseline for central testing of EGFR mutation status and T790M (see Section 5.1.4), patients will be asked to consent to the optional provision of additional tumour material for exploratory research.

A minimum of 3 additional re-cut unstained sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides are preferred. Each section is to be 5 µm thick.

Unused tumour tissue samples will be stored for a period of 15 years unless it is requested to be repatriated. For further details, see the Laboratory Manual.

5.7.2 Collection of tumour biopsy samples at progression

Paraffin embedded tumour tissue will be collected at progression from patients who agreed with this optional assessment and if consent has been obtained for this research. These samples will be sent to a central laboratory for analysis of EGFR mutation status and exploratory biomarker analyses. Samples collected from primary or metastases will be accepted. The investigator will be asked to provide:

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

Unused tumour tissue samples will be stored for a period of 15 years unless it is requested to be repatriated. For further details, see the Laboratory Manual.

5.7.3 Collection of plasma samples for analysis: blood-borne biomarkers and circulating deoxyribonucleic acid

All patients will be requested to provide a series of blood samples to generate plasma samples. These samples will be used for the extraction and analysis of ctDNA. The ctDNA will be used to explore the relationship between emergence of T790M in ctDNA and time to progression. Patients will also be asked to consent for to the use of these samples to further

investigate the relationship between drug response and/or disease progression and blood-borne biomarkers, and to develop blood-based diagnostic tests.

Plasma samples will be taken as described in the Study Plan (see Table 1).

All plasma samples should be sent to AstraZeneca for retrospective analysis. The samples will be analysed for a range of oncology biomarkers, which may correlate with drug response and/or disease progression.

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

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 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 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.

For Japan: For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected. The following should be included if the target disease is progressive: Any deterioration of the disease targeted in the study and associated symptoms should not be regarded as an adverse event as far as the deterioration can be anticipated.

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 including the safety follow-up period. The safety follow-up period is defined as 28 days after study drug is discontinued. Serious AEs occurring in the safety follow-up period should be reported to AstraZeneca in the usual manner (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 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 after progression and during the survival follow-up.

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.

Progression of the malignancy under study, including signs and symptoms progression, should not be reported as a serious adverse event. Hospitalization due to signs and symptoms of disease progression should not be reported as serious adverse event.

6.3.9 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.

6.3.10 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). All SAEs will be recorded in the eCRF.

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 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 28 days 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 1day, 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 28 days 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 5. Gefitinib has no lower dose available.

Table 5 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 **Error! Reference source not found.**.

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade) not attributable to the disease or disease-related processes under investigation, where the Investigator considers the AE of concern to be specifically associated with the study drug 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 **Error! Reference source not found.**. 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.

Recommendations for appropriate management of diarrhoea, including dose adjustments for AEs of diarrhoea that are of CTCAE Grade ≥3 or that are clinically significant and/or intolerable and considered by the Investigator to be causally related to IP, will be provided to Investigators. Changes in CTCAE grade of diarrhoea will be captured in the AE eCRF.

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 2 weeks of onset, study drug may be restarted at the same dose or reduced dose using the dose reduction levels in Table 5 with discussion and agreement with the

AstraZeneca Study Team Physician as needed. If the toxicity does not resolve to ≤CTCAE grade 1 within 2 weeks, the patient will be permanently withdrawn from study drug.

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 should be informed. A questionnaire regarding the results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters) will be sent to the Investigators. 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. 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 permanently discontinued. In the absence of a diagnosis of ILD, study drug may be restarted following consultation with the Study Physician.

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

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 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 6.

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 6 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) or 42 days (Cycle 7 onwards), plus coverage, will be distributed. Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

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.

Any change from the dosing schedule, dose interruptions, or dose reductions should be recorded in the eCRF.

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.

For Japan: Details are specified in the document explaining the reconstitution procedures and other handling procedures for the investigational products.

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.

For Japan: A description of the appropriate storage conditions is specified in the document explaining the reconstitution procedures and other handling procedures for the investigational products.

7.5 Compliance

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.

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.

For Japan: Study drugs will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the study site until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents, 'Procedures for Drug Accountability' and 'Procedures for Drug Storage,' which describe the specific requirements. The Investigator(s) is responsible for ensuring that the patient has returned all unused study drug.

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. Thereafter, only subsequent regimens of anti-cancer therapy will be recored in eCRF. Please see Section 3.8 for restricted concomitant medications during the study.

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.

Use of concomitant medications that may cause QTc prolongation (e.g. anti-emetics) should be avoided (Appendix B). Supportive care and other medications that are considered necessary for the patient's well-being, may be given at the discretion of the Investigator.

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 (not applicable)

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 will be performed when approximately 359 PFS events have occurred. 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. Other secondary efficacy endpoints will be analysed at the time of the PFS analysis, including ORR, DoR, DCR and depth of response.

In addition, a final analysis of OS will be performed at approximately 60% maturity, when approximately 318 death events (across both arms) have occurred. The alpha will be split between the two analyses to provide strong control of the family-wise error rate. The alpha spend function is shown in Figure 1.

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, OS and PFS for the T790M mutation positive subgroup). 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 efficacy.

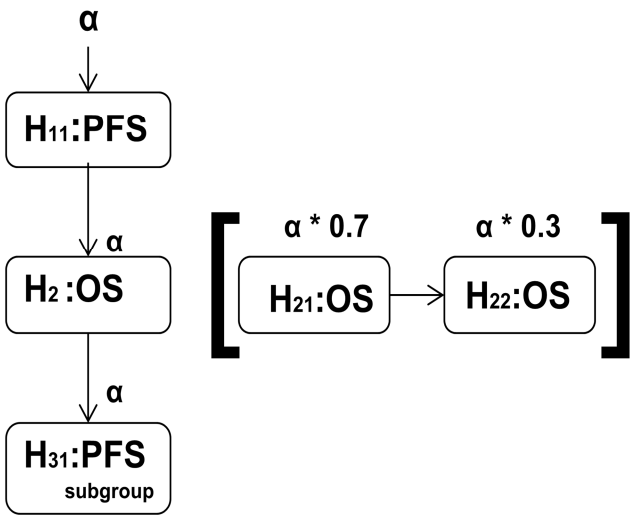
There are 3 overall hypotheses to be tested (endpoints (H_1 PFS, H_2= OS H_3= PFS in subgroup) and 2 analysis time points (t_1 = primary analysis, t_2 = survival follow up) and the alpha will be controlled for testing of the following hypotheses of interest;

H_{11}: PFS (all globally randomized patients) at primary PFS analysis
H_{21}: OS at primary PFS analysis
H_{31}: PFS in T790M+ subgroup at primary PFS analysis
H_{22}: OS at survival follow up

Alpha recycling will be allowed within hierarchical testing, if significance is achieved in a preceding test in the hierarchy.

The following diagram illustrates the strategy for the spending of the test mass (alpha) and shows the order of testing and how the alpha can be used if preceding tests achieve significance (Glimm et al 2010).

Figure 2 Multiple testing diagram



Given that alpha = 0.05 (2-sided), the primary analysis of PFS (all globally randomized patients) will be tested at the full significance level of 0.05. If the primary PFS analysis is significant, then the analysis of OS will be performed. The significance level will be split between the analysis of OS at the time of the primary PFS analysis (α=0.035) and the analysis of OS at the survival follow up (final significance level to be determined accounting for correlation between the interim and final OS analyses (Stone 2010)).

The analysis of PFS and PFS in the T790M subgroup will only be performed once and will not be repeated at the survival follow up. If the OS analysis is significant at the time of the PFS analysis or the final OS analysis, then the significance testing of PFS in the T790M mutation positive subgroup will be performed at the full α=0.05. If the OS analysis is not significant at the time of the PFS analysis or the final OS analysis then the analysis of PFS in the T790M mutation positive subgroup will be not performed.

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 pharmacokineticist 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.

Time from randomisation to second progression (exploratory)

Time from randomisation to second progression (PFS2) is defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression; i.e., censored at the last progression assessment date if the patient has not had a second progression or death.

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 7

Table 7 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 **Error! Reference source not found.**) 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-C30 scales/items).

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

.

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.

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)
- Brain metastases at entry
- Smoking history

8.5.2 Analysis of the secondary variables

8.5.2.1 Hierarchical testing of key secondary variables

The 2 secondary endpoints of PFS in patients with positive pre-treatment T790M status and OS in the overall population will be tested after the primary PFS analysis in a hierarchical procedure at the time of the PFS analysis, following the primary analysis (see Section 8.1).

8.5.2.2 Analysis of progression free survival subgroup

Progression free survival in patients by confirmed pre-treatment T790M status (positive/negative) using a high sensitivity method yet to be determined (retrospective) will be analysed using a Cox Proportional Hazards Model including treatment, race (Asian/Non-Asian), mutation type (Ex19del / L858R), T790M status, and the treatment by T790M status 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 positive patients and separately for negative patients.

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 will be conducted at 2 time points:

- At the time of the primary analysis of PFS.
- At approximately 60% maturity when approximately 318 death events (across both arms) have occurred. 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.

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]).

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

Patient Reported Outcome version of the Common Terminology Criteria for Adverse Event System

Patient Reported Outcome version of the CTCAE data will be presented using summaries and descriptive statistics and further details will be provided in the SAP.

Healthcare Resource Use Module

Healthcare Resource Use data will be presented using summaries and descriptive statistics, based on the FAS and further details will be provided in the SAP.

Exploratory analysis of post-progression outcomes

Second progression free survival will be analysed using the same method as the analysis of PFS. Time to first subsequent therapy and time to second subsequent therapy will be summarised as appropriate and further details will be provided in the SAP.

Exploratory analysis of characterising survival

All further analysis of OS will be exploratory. The effect of baseline characteristics on OS in each randomised treatment arm will be summarised. As appropriate, time-varying outcomes measured during the study treatment and post progression phases will also be summarised. All subsequent treatments in each treatment arm will be summarised, including duration of treatments. For summaries, anti-cancer treatments will be grouped by mode of action (e.g., $1^{st}/2^{nd}$ generation EGFR-TKIs, 3^{rd} generation EGFR-TKIs with T790M activity [e.g., AZD9291, others], platinum-based doublet chemotherapy, single agent chemotherapy).

Further detail will be provided in the SAP.

Summaries and analyses for other exploratory objectives will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

8.6 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 and analysed separately. 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 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.

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.

For Japan: Source data are any data generated as a result of the patient's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records. Original data recorded on the eCRFs and regarded as source data are electronic medical charts and worksheets.

9.2.2 Direct access to source data in Japan

The Head of the study site and the Principal Investigator/Investigator will cooperate for monitoring and audit by AstraZeneca, and accept inspection by the Institutional Review Board (IRB) or regulatory authorities. All study documents such as raw data will be opened for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the eCRFs against source data before the Principal Investigator signs the eCRFs to ensure accuracy and completeness of documentation.

9.2.3 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.

For Japan: The Principal Investigator at each study site should comply with all the terms, conditions, and obligations of the Study Agreement with the Principal Investigator, or equivalent, for this study. In the event of any inconsistency between this CSP and the Study Agreement with Principal Investigator, 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 Study Agreement with Principal Investigator shall prevail. Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or any patients are enroled.

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

For Japan (through Section 9.2.5):

Study files. *AstraZeneca will provide the Principal Investigator with a file in which to organise and retain all study-related documents. All study documents (including letters from AstraZeneca) should be retained in this file by the Principal Investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by AstraZeneca's auditor, regulatory authorities, or IRB.*

Period of record retention*. The study site (and the Principal Investigator) will retain the essential documents specified in the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) (e.g., source document such as medical records, contract, signed consent form). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with AstraZeneca. However this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by AstraZeneca, and the specific period and method of retention will be separately discussed between the study site and AstraZeneca. AstraZeneca should notify the head of the study site in writing when the study related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.*

9.2.5 Deviation from the Clinical Study Protocol

For Japan:

The Investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the Principal Investigator and AstraZeneca or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the patients or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical study (e.g., changes to the organisation/structure of AstraZeneca, the name/department name of the study site, the address or phone number of the study site or AstraZeneca, the job title of the Investigator, and monitors).

The Investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the patients or for other medically compelling reason, the Investigator should prepare and submit the records explaining the reasons thereof to AstraZeneca and the head of study site, and retain a copy of the records.

The Investigator(s) may deviate from or make a change to the protocol without documented agreement between the Principal Investigator and AstraZeneca or the IRB approval, only in the event of a medical emergency, e.g., it is the only way to avoid an immediate hazard to the patients. In such case, the Principal Investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to AstraZeneca and the head of the study site and IRB via the head of the study site as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca should be obtained via the head of the study site.

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 2018.

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.

For Japan:

Planned duration of the study:

Study period: October, 2014 - April, 2018

Discontinuation or suspension of the whole study programme

If AstraZeneca decides to prematurely terminate or suspend the study, the Principal Investigator/Investigator, the head of the study site, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.

The Principal Investigator/Investigator will immediately notify the decision to the patients, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

Completion of the study

Upon terminating the study, the Principal Investigator/Investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the study site's rules. The head of the study site, who is informed of the termination by the Investigator, will provide a written notification of the results to the IRB and AstraZeneca.

9.4 Data management by AstraZeneca (or delegate)

Data management will be performed by , 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 .

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 .**

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.

For Japan: The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs' (Ministry of Health, Labor and Welfare [MHLW] Ordinance No. 28, 27 March 1997), partially revised by MHLW Ordinance and their related notifications.

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.

For Japan:

The Master Informed Consent Form will explain that:

- *Study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation.*
- *Patient data will be maintaining confidentiality in accordance with national data legislation.*

- *For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an IRB may require direct access to parts of the hospital or practice source records relevant to the study, including patients' medical history.*
- *All data computer processed by AstraZeneca will be identified by study code and enrolment code (E-code).*

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.

For Japan:

An 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 head of the study site will ensure the distribution of these documents to the applicable IRB, and the Principal Investigator to the Investigator and study site staff.

The opinion of the IRB should be given in writing. The head of the study site should submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca and the Principal Investigator before enrolment of any patient should into the study.

The 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.

A valid contract between the study site and AstraZeneca should be signed before the Investigator can enrol any patient into the study. The protocol should be re-approved by the IRB annually.

The head of the study site should seek the opinion of the IRB with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds one year. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority with notification provided, according to local regulations. AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, IRB, the head of the study site and the Principal Investigator with safety updates/reports according to local requirements.

The head of the study site should submit a written report to the IRB providing the details of all safety relative information reported by AstraZeneca.

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.

For Japan:

If any new information on the study drug *becomes available which may influence the decision of the patient to continue the study, the Investigator(s) should inform the patient of such information immediately, record this in a written form, and confirm with the patient if he or she wishes to continue the participation in the study. In addition, if the Investigator(s) deem it necessary to revise the ICF, they should revise it immediately (Refer to Section 10.5). The Investigator(s) should re-explain to the patients using the updated ICF even though the patients have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.*

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

The amendment is to be approved by the relevant EC/IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to EC/IRB see Section 10.3.

If a protocol amendment 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.

For Japan:

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the

amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular site's ICF, then AstraZeneca and the site's IRB should be notified. Approval of the revised ICF by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

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.

For Japan: All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

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