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Clinical Study Protocol	
Drug Substance	AZD9291
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A Phase III, Open Label, Randomized Study of AZD9291 versus Platinum-Based Doublet Chemotherapy for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and whose Tumours harbour a T790M mutation within the Epidermal Growth Factor Receptor Gene (AURA3)

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VERSION HISTORY

Version 5, January 10, 2017

The reason for this protocol amendment is to update the clinical study protocol to:

- Amend the data collection and criteria for potential crossing-over post primary PFS analysis
- Outline patient management post final OS analysis (at approximately 70% maturity)
- In addition, the protocol has been updated to reflect changes in the Investigator's Brochure (IB) Version 6 update (detailed in the Version History section) regarding the management of toxicities and pregnancy

The primary, secondary and exploratory objectives of this protocol remain unchanged, and no inclusion or exclusion criteria were added, changed or deleted.

The details of the changes are summarized below:

1. Post primary PFS analysis, the data collection schedule will be reduced to key variables such as overall survival, patient reported outcomes and safety. Subjects still on the platinum-based doublet chemotherapy arm will be given the opportunity to begin treatment with AZD9291 80mg, once daily at the discretion of the investigator.
2. Following the final OS analysis (at approximately 70% maturity), access to treatment will continue to be assured for patients still receiving AZD9291. Patients still receiving therapy will be permitted to continue to receive study treatment if, in the opinion of the investigator, they are continuing to receive benefit from treatment. Patients who remain on study treatment after this time point will be monitored according to routine clinical practice as defined by the Investigator, and will continue to report all SAE, overdose and pregnancy information.

Note: Study assessments and data collection will continue at each site according to CSP Version 4, dated 21 March 2016 until this CSP version is approved by the health authority and/or IRB/IEC, in accordance with local requirements. The analysis and reporting of these data will be performed according to this CSP version.

Major changes to the protocol are summarised below:

- Protocol synopsis (study design and duration of treatment) was updated to clarify the requirements up to the primary PFS analysis and then post primary PFS analysis. Following the primary PFS analysis subjects still on the platinum-based doublet chemotherapy arm will be given the opportunity to begin treatment with AZD9291 80 mg, once daily if it is considered by the Investigator to be in the patient's best interest, and if they are eligible to

receive AZD9291 (no contraindications).

- Section 1.3 (Rationale for study design, doses and control groups) and Section 1.5 (Study design) were updated to clarify the requirements up to the primary PFS analysis and then post primary PFS analysis. Following the primary PFS analysis subjects still on the platinum-based doublet chemotherapy arm will be given the opportunity to begin treatment with AZD9291 80 mg, once daily if it is considered by the Investigator to be in the patient's best interest, and if they are eligible to receive AZD9291 (no contraindications).

- Section 3.7.1 (Procedures for discontinuation of a subject from study treatment): clarification has been added that, following the primary PFS analysis, tumour assessments will no longer be collected apart from patients in China.

- Section 4 (Table 1, Table 2 and Table 3): the table title was updated to specify that the study plan outlined in Table 1, Table 2 and Table 3 is valid up to primary PFS analysis.

- Section 4 (Table 4): table added to outline the study plan post primary PFS analysis until the final OS analysis DCO. The data collection will be reduced to key variables such as overall survival, patient reported outcomes and safety. The central ECG, information for PFS2 and health care resource use will continue until the first OS analysis DCO.

- Section 4.2 (treatment period) and Section 4.3 (follow-up period): the sub-section titles were updated to specify that the study assessment and data collection are valid up to primary PFS analysis.

- Section 4. 3. 5 (Patient management post primary PFS analysis): section added to provide more detail regarding the management of patients after primary PFS analysis.

- Section 4.3.6 (Patient management post final OS analysis): section added to provide more detail regarding the management of patients after the final OS analysis DCO.

- Section 5.1 (efficacy assessments): section was modified to clarify that post primary PFS analysis, subjects still on the platinum-based doublet chemotherapy arm will be given the opportunity to begin treatment with AZD9291 80mg, once daily at the discretion of the investigator and tumour assessment will be performed in accordance with clinical practice and scans will no longer be centrally collected apart from patients from China.

- Section 5.2.4 (ECG): section was modified to clarify that post the first OS analysis DCO ECGs will be performed according to routine clinical practice, locally and stored at the site. ECG information (evaluation of normal/abnormal) will continue to be recorded in the eCRF. After final OS analysis, ECGs will be performed according to routine clinical practice.

- Section 5.2.5 (Echocardiogram/MUGA scan): section was modified to clarify that post final OS analysis, Echocardiogram/MUGA scan will be performed clinically indicated as necessary by the Investigator.

- Section 5.3.2 (Patient reported outcomes): section was modified to clarify that the PRO data

collection will be collected until the end of study (including survival follow-up period) and at the time of progression, unless consent is withdrawn or patient is lost to follow up, as indicated in the Study Plan.

- Section 5.3.2.5 (Healthcare resource use): section was modified to clarify that healthcare resource use information will continue to be collected until the first OS analysis DCO. After the first OS analysis DCO, this information is not required to be collected.

- Section 5.6.2 (Collection of exploratory samples): section was modified to clarify that post primary PFS analysis, ctDNA samples will continue to be collected at treatment discontinuation and at progression.

- Section 5.8 (Post progression outcomes): section was modified to clarify PFS2 is only required to be collected up to the first OS analysis DCO. After the first OS analysis DCO, this information is not required to be collected.

- Sections 6.3.1 (Time period for collection of adverse events) and 6.4 (Reporting of serious adverse events): sections were modified to provide more clarity regarding the process of collecting SAE, overdose and pregnancy information after final OS DCO.

- Section 6.6 (Pregnancy): section was modified to reflect the Investigator's Brochure (IB) Version 6 update.

- Section 6.7 (Management of toxicities related to AZD9291): section was modified to reflect the Investigator's Brochure (IB) Version 6 update.

- Section 7.1 (Identity and Dose of investigational product – AZD9291) and 7.5 (Compliance): sections were updated to provide more clarity regarding the drug dispensing and drug accountability process after final OS analysis DCO.

- Section 7.8 (Post access to study treatment): section was updated to provide more clarity about the management of patients at the time of study completion after the final OS DCO.

Version 4, 21 March 2016
Refer to Amendment #3 document for details

Version 3, 06 May 2015
Refer to Amendment #2 document for details

Version 2, 22 Dec 2014
Refer to Amendment #1 document for details

Version 1.1, 18 July 2014
Refer to Administrative Change #1 document for details

Version 1, 6 May 2014
Initial creation

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.

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PROTOCOL SYNOPSIS

A Phase III, Open Label, Randomized Study of AZD9291 versus Platinum-Based Doublet Chemotherapy for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and whose Tumours harbour a T790M mutation within the Epidermal Growth Factor Receptor Gene (AURA3)

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Study site(s) and number of subjects planned

Approximately 410 subjects will be randomized from 19 countries across approximately 160 centres in North America, Asia and Europe. Once 410 subjects have been randomized globally, recruitment will continue only in mainland China until approximately 50 Chinese subjects have been randomized.

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2014	III
Estimated date of last subject completed	Q4 2018	

Study design

This is a phase III, open-label, randomized study assessing the safety and efficacy of AZD9291 (80 mg, orally, once daily) versus platinum-based doublet chemotherapy in patients with Epidermal Growth Factor Receptor Mutation and T790M Mutation Positive (EGFRm+/T790M+), locally advanced or metastatic NSCLC who have progressed following treatment with an approved Epidermal Growth Factor Tyrosine Kinase Inhibitor (EGFR-TKI) agent.

In order to randomize approximately 410 subjects it is expected that an estimated 1034 subjects will be screened. Once 410 subjects have been randomized globally, recruitment will continue only in mainland China until approximately 50 Chinese subjects have been randomized.

A biopsy will be needed for central testing of T790M mutation status following confirmed disease progression on first line treatment with an EGFR TKI.

Suitable subjects will then be randomized to receive either AZD9291 (80mg orally, once daily) or platinum-based doublet chemotherapy (pemetrexed 500 mg/m^2 + carboplatin area under the plasma concentration–time curve AUC 5 or pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2) on Day 1 of every 21-day cycle in a 2:1 (AZD9291: platinum-based doublet chemotherapy) ratio.

Subjects should continue on investigational product AZD9291 until a treatment discontinuation criterion is met. Subjects may continue to receive AZD9291 beyond RECIST 1.1 defined progression as long as they are continuing to show clinical benefit, as judged by the investigator.

Subjects can receive up to 6 cycles of pemetrexed + carboplatin/cisplatin as initial treatment. Subjects whose disease has not progressed after four cycles of platinum-based first-line chemotherapy may receive pemetrexed maintenance therapy. Subjects who progress according to RECIST 1.1 criteria prior to completion of initial doublet chemotherapy treatment or during pemetrexed maintenance monotherapy, may continue with chemotherapy treatment as long as they show clinical benefit, as judged by the investigator.

Up to the primary PFS analysis, subjects must be followed until evidence of RECIST 1.1 defined progression (regardless of reason for treatment discontinuation). It is important that subjects 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.

Up to the primary PFS analysis, once subjects on the platinum-based doublet chemotherapy arm are determined to have objective radiological progression according to RECIST 1.1 by the investigator and confirmed by independent central imaging review, they will be given the opportunity to begin treatment with AZD9291 80mg, once daily. These subjects may continue treatment with AZD9291, as long as they show clinical benefit, as judged by the investigator.

Up to the primary PFS analysis, if a subject has been deemed to have objective disease progression according to Investigator tumour assessment by RECIST 1.1, but is not confirmed by independent central imaging review, he/she is not eligible to cross-over to AZD9291 at that time. Should it be in the subject's best interest, and only if further randomized chemotherapy is warranted, he/she may continue to receive randomized doublet chemotherapy (if initial doublet chemotherapy treatment has not yet been completed) or pemetrexed maintenance monotherapy. Sites are to submit the next scheduled tumour assessment for central imaging review according to Table 2.

Following the primary PFS analysis subjects still on the platinum-based doublet chemotherapy arm will be given the opportunity to begin treatment with AZD9291 80mg, once daily if it is considered by the Investigator to be in the patient's best interest, and if they are eligible to receive AZD9291 (no contraindications). At least a 14 day washout period is required between last dose of chemotherapy and starting AZD9291 treatment.

If subjects randomised to chemotherapy are not eligible to receive AZD9291, they will enter into the follow-up phase of the study, and other treatment options should be discussed by the investigator.

Note: Throughout this document,

1. The study design and assessments required are only applicable for the period up to the primary PFS analysis unless indicated otherwise.

2. The term "platinum-based doublet chemotherapy", refers to "platinum" as both carboplatin and cisplatin.

Objectives

Primary Objective:	**Outcome Measure:**
To assess the efficacy of AZD9291 compared with platinum-based doublet chemotherapy by assessment of Progression Free Survival (PFS).	Progression Free Survival (PFS) using investigator assessments according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1). Sensitivity analysis of Progression Free Survival using Blinded Independent Central Review (BICR).

Secondary Objective:	**Outcome Measure :**

To further assess the efficacy of AZD9291 compared with platinum-based doublet chemotherapy in terms of: - Objective Response Rate (ORR) - Duration of Response (DoR) - Disease Control Rate (DCR) - Tumour shrinkage - Overall Survival (OS)	ORR, DoR, DCR and tumour shrinkage using investigator assessments according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1). Analysis of overall survival.
To assess the effect of AZD9291 compared to platinum-based doublet chemotherapy on subjects' disease-related symptoms and health related quality of life (HRQoL).	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13). EORTC QLQ-C30: Questionnaire consisting of 30 items measuring subjects general cancer symptoms and functioning. EORTC QLQ-LC13: A complementary questionnaire measuring lung cancer symptoms.
To characterise the pharmacokinetics (PK) of AZD9291 and metabolites in subjects receiving AZD9291.	PK exposure parameters derived from plasma concentrations of AZD9291, and metabolites AZ5104 and AZ7550. PK Parameters (CLss/F, Css, min and Css, max AUCss) will be derived using population PK analysis and reported separately to the CSR. Data from this study may form part of a pooled analysis with data from other studies.

Safety Objective:	**Outcome Measure :**
To assess the safety and tolerability profile of AZD9291 compared with platinum-based doublet chemotherapy.	Adverse events (graded by Common Terminology Criteria for Adverse Event (CTCAE v4) - Clinical chemistry, haematology and urinalysis - Vital signs (pulse and blood pressure), Physical Examination, Weight - Centrally reviewed digital Electrocardiogram (ECG) - Echocardiogram/ Multi Gated Acquisition Scan (MUGA) (for Left Ventricular Ejection Fraction) - World Health Organization (WHO) performance status

Exploratory Objectives:	**Outcome Measure:**
To explore the relationship between PK and selected endpoints (which may include efficacy, safety and/or Patient Reported Outcome [PRO]), where deemed appropriate.	Correlation of PK with other primary /secondary/ exploratory endpoints in subjects treated with AZD9291. Results from such analyses will be reported separately from the Clinical Study Report (CSR). Data from this study may also form part of a pooled analysis with other AZD9291 studies.
To compare the effects of AZD9291 compared with chemotherapy on post progression outcomes	Time from randomization to second progression (PFS2) Time to subsequent treatments Time to change in symptoms (including post progression assessments)
To further characterise the effects of AZD9291 on survival outcomes.	Assess the impact on overall survival of baseline potentially prognostic factors (e.g. tumour stage, performance status, sex, baseline lactate dehydrogenase [LDH]) Assess the impact on OS of subsequent treatments and other potential covariates (e.g. changes in performance status)
To compare adverse events by subject self-reporting of specific CTCAE symptoms (where applicable) between AZD9291 and chemotherapy.	Collection of approximately 28 PRO-CTCAE symptoms via an electronic device solution (in countries where language is available).

Exploratory Objectives:	**Outcome Measure:**
To compare AZD9291 treatment with chemotherapy treatment on health state utility.	The EQ-5D-5L health state utility index will be used to derive health state utility based on subject reported data.
To compare health resource use associated with AZD9291 treatment with chemotherapy treatment.	Health resource utilisation measures including hospitalization, outpatient visits, or emergency department visits.
To characterise the pharmacokinetics (PK) of AZD9291and metabolites in cerebrospinal fluid (CSF).	Concentration of AZD9291, AZ5104 and AZ7550. Ratio of metabolites to AZD9291. Ratio of CSF to plasma concentration. Summaries of PK concentration data.
To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence PK or response to AZD9291, platinum-based doublet chemotherapy (ie, absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers.	Correlation of polymorphisms with variation in Pharmacokinetics (PK), Pharmacodynamics (PD), safety or response observed in subjects treated with AZD9291 or comparator. Data generated may be reported separately and may also form part of a pooled analysis with other AZD9291 studies.
To collect and store tumour samples and blood-based samples for potential for exploratory research into factors that may influence susceptibility to/development of NSCLC/cancer and/or response to AZD9291 (where response is defined broadly to include efficacy, tolerability or safety).	Analysis of key genetic and proteomic markers to include, but not limited to, EGFR mutations, Human Epidermal Growth Factor Receptor 2 (HER2) & CMET expression and/or amplication. Collection of plasma samples to include, but not be limited to, extraction of circulating tumour DNA (ctDNA) for investigation of blood borne biomarkers. The sample may be used to investigate the relationship between PK and blood-borne biomarkers. Samples may be analysed retrospectively. Any biomarker data generated may be reported separately and may also form part of a pooled analysis with other AZD9291 studies.

Exploratory Objectives:	Outcome Measure:
To collect and store plasma for isolation of ctDNA. Extracted ctDNA will be assessed for the presence of genetic abberations including, but not limited to, EGFR mutations (T790M, L858R, etc). These samples may be shared with a diagnostic partner for development of a ctDNA test for T790M detection.	Retrospective/real-time analysis of EGFR (and other) mutations in ctDNA from all study subjects (mandatory).
To collect and store residual CSF for potential exploratory research of factors that may influence development of NSCLC and/or response to AZD9291 (where response is defined broadly to include efficacy, tolerability or safety).	Collection of CSF for the investigation of PK and/or biomarkers. Samples may be analysed retrospectively.

Target subject population

Male and female subjects aged 18 years and over (subjects from Japan aged at least 20 years) who have histologically or cytologically proven NSCLC that is locally advanced or metastatic and not amenable to further surgery or radiotherapy with curative intent and whose disease has progressed with previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy.

Subjects must be eligible to receive treatment with the selected platinum–based doublet chemotherapy (pemetrexed + cisplatin /carboplatin) in accordance with local prescribing information and have documentation of EGFR Mutation (at any time since a diagnosis of NSCLC was made) and T790M Mutation positive tumour. Subjects must have measurable disease (using Computer Tomography [CT]/Magnetic Resonance Imaging [MRI]) as defined by RECIST 1.1 guidelines and WHO Performance Status of 0-1.

Duration of treatment

Treatment with AZD9291 80 mg, once daily, will commence following randomization. Subjects may continue to receive treatment with AZD9291 as long as they are continuing to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria (see Section 3.7).

Treatment with intravenous platinum-based doublet chemotherapy (on Day 1 of every 21 day cycle) will commence following randomization up to a total of 6 cycles. Patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy may receive pemetrexed maintenance therapy.

Subjects who progress according to RECIST 1.1 criteria prior to completion of initial doublet chemotherapy treatment or during pemetrexed maintenance monotherapy, may continue with treatment as long as they show clinical benefit, as judged by the investigator.

Up to the primary PFS analysis, once subjects on the platinum-based doublet chemotherapy arm are determined to have objective radiological progression according to RECIST 1.1 by the investigator and confirmed by independent central imaging review, they will be given the opportunity to begin treatment with AZD9291 80mg, once daily. These subjects may continue treatment with AZD9291 as long as they show clinical benefit, as judged by the investigator. If a subject has been deemed to have objective disease progression according to Investigator tumour assessment by RECIST 1.1, but is not confirmed by independent central imaging review, he/she is not eligible to cross-over to AZD9291 at that time. Should it be in the subject's best interest, and only if further randomized chemotherapy is warranted, he/she may continue to receive randomized doublet chemotherapy (if initial doublet chemotherapy treatment has not yet been completed) or pemetrexed maintenance monotherapy. Sites are to submit the next scheduled tumour assessment for central imaging review according to Table 2.

Following the primary PFS analysis subjects still on the platinum-based doublet chemotherapy arm will be given the opportunity to begin treatment with AZD9291 80mg, once daily if it is considered by the Investigator to be in the patient's best interest, and if they are eligible to receive AZD9291 (no contraindications). At least a 14 day washout period is required between last dose of chemotherapy and starting AZD9291 treatment.

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 will be administered orally as one 80 mg tablet once a day. A cycle of treatment is defined as 21 days of once daily AZD9291 treatment.

Comparator product, dosage and mode of administration

Platinum-based doublet chemotherapy will be administered intravenously on Day 1 of every 21-day cycle of either:

- Pemetrexed 500mg/m^2 + carboplatin AUC5.

  Or

- Pemetrexed 500mg/m^2 + cisplatin 75mg/m^2.

In order to reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4mg of dexamethasone administered orally twice a day.

To reduce toxicity, subjects treated with pemetrexed must also receive vitamin supplementation. Subjects must take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Subjects must also receive an intramuscular injection of vitamin B12 (1,000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed. Subjects may also receive other pre-

treatment / concomitant treatment as recommended by approved label for pemetrexed, carboplatin or cisplatin as clinically indicated by the investigator.

The wash out period between stopping the randomized chemotherapy and starting AZD9291 80mg, once daily, in subjects eligible for cross-over is at least 14 days. 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.

Statistical methods

Subjects will be randomized to the trial in a 2:1 ratio:

- AZD9291 80mg will be administered orally once a day

  Or

- Platinum-based doublet chemotherapy will be administered intravenously on Day 1 of every 21-day cycle of either:
  - pemetrexed 500mg/m^2 + carboplatin AUC5

    Or

  - pemetrexed 500mg/m^2 + cisplatin 75mg/m^2

Subjects will be stratified at randomization based on ethnicity (Asian/Non-Asian).

PFS is the primary endpoint for this study. Approximately 410 subjects will be randomized in a 2:1 ratio (AZD9291: platinum-based doublet chemotherapy) in this study.

The primary analysis of PFS will occur when at least 221 progression events have been observed out of the 410 globally randomized subjects. With 221 progression events, the study will have at least 80% power to show a statistically significant PFS at the 5% 2-sided significance level if the assumed treatment effect were HR 0.67; this translates to a 3 month improvement on an estimated median PFS of 6 months on the control arm, assuming PFS is exponentially distributed. The smallest treatment difference that would be statistically significant is a PFS HR of 0.76 (this translates into an approximate 2 month improvement on an estimated median PFS of 6 months on the control arm, assuming PFS is exponentially distributed). Assuming 15 months non-linear recruitment, 221 PFS events are expected to occur approximately 20 months after the first subject is randomized in the study.

Three analyses of overall survival will be conducted. The data cut-off for the first analysis will be performed approximately 4 months after data cut-off for the primary analysis of PFS, and the second analysis will be performed when the OS data are approximately 50% mature (approximately 205 death events). The final (third) analysis of overall survival will be performed when the OS data are approximately 70% mature (approximately 287 death events).

PFS will be analyzed using a log rank test stratified by ethnicity (Asian, Non-Asian). The primary PFS analysis will be based on investigator-recorded assessment of disease progression by RECIST; a sensitivity analysis will also be performed using a blinded independent central review (BICR).

Secondary endpoints of ORR, DoR, DCR and Tumour Shrinkage will be analyzed at the time of the primary PFS analysis. OS will be summarised only at the time of the primary analysis (a summary of the frequency of deaths and primary cause of death will be provided for safety purposes); the analysis of OS will be performed approximately 4 months after the data cut-off for the primary analysis of PFS.

In order to provide strong control of the type I error rate (2-sided 5%), the primary endpoint (PFS) and key secondary endpoints (ORR and OS) will be tested in a sequential order. If any previous analysis in the sequence is not statistically significant, the alpha spending cannot be transferred to subsequent analyses. Since three OS analyses are planned, the Lan DeMets approach that approximates the O'Brien and Fleming spending function will be used to maintain an overall 2-sided 5% type I error across the testing of three planned analyses of OS.

The safety and efficacy data collected for Chinese subjects from mainland China after global recruitment has closed will be combined with data from the Chinese subjects recruited prior to the end of global recruitment, and summarised and analysed separately. This China cohort will provide standalone safety and efficacy analyses of subjects from China and will be reported separately from the Clinical Study Report. These analyses may be performed at the time of the primary PFS analysis if at least 20 PFS events have been observed out of approximately 50 Chinese subjects, otherwise summaries of efficacy will be provided only. Additional follow-up of Chinese subjects if deemed appropriate may be performed when the PFS data are more mature (for example, 70% maturity, as consistent with the primary global PFS analysis).

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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
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AnLK	Anaplastic lymphoma kinase
ANSM	Agence Nationale de Securite du Medicaments
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AUC	Area under the curve (plasma concentration / time curve)
AUC5	Area under the plasma concentration–time curve 5 mg/ml per minute
AUC (0-24)	Area under the curve (plasma concentration / time curve from zero to 24 hours)
AUCss	Plasma Clearance at Steady State
AZ	AstraZeneca
BCRP	Breast Cancer Resistance Protein
BICR	Blinded Independent Central Review
BoR	Best Overall Response
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood urea nitrogen
CI	Confidence Interval
CK	Creatine Kinase
CLss/F	Plasma Clearance at Steady State
Cmax	Maximum plasma concentration
CMET	Proto-oncogene encoding Hepatocyte Growth Factor Receptor
CR	Complete response
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organization

Abbreviation or special term	Explanation
CSA	Clinical Study Agreement
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
Css	Concentration at Study State
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Event
*ct*DNA	Circulating tumour Deoxyribonucleic acid
CYP	Cytochrome P450
DAE	Discontinuation of Investigational Product due to Adverse Event
DCO	Data cut off
DCR	Disease Control Rate
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DoR	Duration of Response
DUS	Disease under Study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EDoR	Expected Duration of Response
EGFR	Epidermal Growth Factor Receptor
EGFRm+	EGFR Mutation positive
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items
EORTC QLQ LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items
EU	European Union
Ex19Del	Deletions in exon 19
FDA	Food and Drug Administration
FFPE	Formalin Fixed and Paraffin Embedded
FFST	Time to First Subsequent Therapy or Death
FSH	Follicle-Stimulating Hormone
FSI	First Subject In

Abbreviation or special term	Explanation
G719X	An in-frame amino acid (glycine (G)) deletion at position 719 in EGFR
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HDPE	High-Density-Polyethylene
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICR	Independent Central Review
ILD	Interstitial Lung Disease
INR	International Normalized Ratio
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
IUS	Intra Uterine System
iv	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
LDH	Lactate Dehydrogenase
LDL	Low-density Lipoprotein
LH	Luteinizing Hormone
LSLV	Last Subject Last Visit
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Medical Products Agency
MRI	Magnetic resonance imaging

Abbreviation or special term	Explanation
MUGA	Multi Gated Acquisition Scan
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-Small Cell Lung Cancer
NTL	Non-target Lesion
NYHA	New York Heart Association
OAE	Other Significant Adverse Event
ORR	Objective Response Rate
OS	Overall Survival
P	Probability
PD	Progression of disease
PD	Pharmacodynamics
PFS	Progression Free Survival
PFSs	Time from Randomization to Second Progression
PGx	Pharmacogenetic research
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial Response
Pre-treatment:	Medication used before chemotherapy, e.g., folic acid, corticosteroid and vitamin B12 or anti-emetic drugs according to the respective chemotherapy local labels (cisplatin, carboplatin and pemetrexed).
Pre-medication:	Medication used to prevent study drug side effects, for example, to treat diarrhoea once it is detected, and used as long as needed. It can also be used prophylactically in case subjects are prone to develop a particular adverse event.
PRO	Patient Reported Outcome
QD	Once daily
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 on Multiple Dosing
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RR	Response Rate
SAE	Serious adverse event

Abbreviation or special term	Explanation
SAP	Statistical Analysis Plan
SD	Stable disease
SDV	Source Data Verification
SoC	Standard of Care
SPC	EU Summary of Product Characteristics
T790M	An amino acid substitution at position 790 in EGFR, from a Threonine (T) to a Methionine (M)
T790M+	T790M mutation positive
TKI	Tyrosine Kinase Inhibitor
TL	Target Lesion
tmax	Time to Cmax
tss max	Time to Css max
TSST	Time to Second Subsequent Therapy or Death
ULN	Upper Limit of Normal
US	United States
WBDC	Web Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

1.1 Non-small Cell Lung Cancer (NSCLC)

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total) (GLOBOCAN 2008). NSCLC represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of NSCLC patients already have 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).

Treatment of advanced NSCLC can be guided by the presence of certain molecular drivers such as EGFR, anaplastic lymphoma kinase (AnLK) and KRAS mutations. The incidence of Epidermal Growth Factor Receptor mutation positive (EGFRm+) NSCLC is approximately 10-15% and 30-40% of patients in the West and Asia, respectively.

Although first- (eg, erlotinib, gefitinib) and second-generation (eg, afatinib) Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKIs) are established therapies for patients with NSCLC known to have activating mutations in EGFR (EGFRm+), the emergence of a secondary T790M mutation in patients treated with an EGFR TKI agent has been described as a major route of development of resistance to this class of therapy (Pao et al 2005, Kobayashi et al 2005) in approximately 60% of patients (Yu et al 2013).

In the advanced NSCLC post-EGFR TKI treatment failure setting, prolonged survival rates remain very low (median OS in the region of 1 to 2 years, Wang et al 2012, Wu et al 2010, Fukuoka et al 2011). No approved therapy is currently available for patients with T790M mutation positive (T790M+) tumours that have acquired EGFR TKI resistance or refractoriness. There is no data on response rates (RRs) with single agent chemotherapy in the specific subset of T790M+ patients after failure of EGFR TKI.

Treatment guidelines for 2nd line treatment of EGFRm+ NSCLC include using platinum based chemotherapy doublet treatment (e.g. U.S. NCCN 2012 guidelines). Second-line platinum-based chemotherapy post EGFR TKI for EGFRm+ NSCLC generally provides RRs in the range of 20 to 30% (Gridelli et al 2012, Goldberg et al 2012, Maemondo et al 2010, Wang et al 2012, Wu et al 2010). Although slightly better than the RRs that can be expected with single-agent chemotherapy in later lines, these data together with the toxicity burden associated with doublet chemotherapy (that includes nausea, vomiting, bone marrow suppression resulting in high risk of infection and bleeding, alopecia, fatigue, and peripheral neuropathy) confirm the unmet medical need that exists in this patient population.

1.2 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 sensitivity mutations (the most common of which are L858R 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. In approximately 60% of these initially EGFR-TKI responsive patients (Yu et al 2013), disease progression is associated with the emergence of a secondary EGFR mutation, T790M in exon 20 of EGFR, which confers resistance to EGFR-TKI therapy (Pao et al 2005). The T790M resistance mutation is located in the hinge region of the kinase domain of the adenosine triphosphate (ATP) binding pocket of the EGFR protein, where the bulky methionine side chain prevents binding of the EGFR-TKIs (Heuckmann et al 2012).

AZD9291 is a potent irreversible inhibitor of both the single EGFRm+ (TKI sensitivity conferring mutation) and dual EGFRm+/T790M+ (TKI resistance conferring mutation) receptor forms of EGFR with a significant selectivity margin over wild-type EGFR. Therefore AZD9291 has the potential to provide clinical benefit to patients with advanced NSCLC harbouring both the single sensitivity mutations and the resistance mutation following prior therapy with an EGFR-TKI. The clinical development programme with AZD9291 will initially assess the safety and efficacy of AZD9291 in patients with advanced NSCLC whose cancers have progressed following an EGFR-TKI regimen (with or without additional chemotherapy regimens), as they currently represent a major unmet medical need population. Importantly, preliminary data from an ongoing phase I study (D5160C00001) in this patient population has demonstrated good evidence of efficacy in patients who have progressed on or after an approved EGFR TKI only or additional therapies (≥ 2nd line), while treatment with AZD9291 has been well tolerated across a range of doses (refer to the latest edition of the Investigator Brochure for further details) (Ranson et al WCLC 2013).

1.3 Rationale for study design, doses and control groups

At the time this protocol was written (May 2014), no approved therapies existed to specifically target T790M+ acquired EGFR-TKI resistance, which represents the most common resistance mechanism in the majority of NSCLC patients with acquired EGFR-TKI resistance. The purpose of this study is to further characterise and confirm the efficacy and safety of AZD9291 in EGFRm+/T790M+ NSCLC patients who have acquired resistance to an EGFR-TKI (and who are chemotherapy naive) observed in the ongoing phase I study (D5160C00001).

The majority of patients with EGFRm+ NSCLC respond well initially to treatment with EGFR-TKIs with an Objective Response Rate (ORR) of approximately 60 to 70%, but eventually develop resistance with a median time to progression of around 9-11 months. In at

least half of initially TKI-responsive patients, disease progression is associated with the emergence of a secondary EGFR mutation, called T790M mutation in exon 20 of the EGFR gene. There are no current effective recommended standard of care therapies for these NSCLC patients with acquired EGFR-TKI resistance who are T790M+. Treatment guidelines for 2nd line treatment of EGFRm+ NSCLC include using platinum based chemotherapy doublet treatment (e.g. NCCN 2012).

A commonly used platinum doublet is pemetrexed in combination with cisplatin or carboplatin. Pemetrexed in combination with cisplatin demonstrated superior OS compared to Gemcitabine in combination with cisplatin in previously untreated advanced NSCLC patients with non-squamous histology (adenocarcinoma and large cell carcinoma) in a randomised phase III trial: 12.6 vs. 10.9 (with adenocarcinoma) and 10.4 vs 6.7 months (with large-cell carcinoma) respectively (Scagliotti et al 2008). Pemetrexed in combination with cisplatin reported lower rates of grade 3 or 4 neutropenia, anaemia, thrombocytopenia, febrile neutropenia and alopecia, and higher rates of grade 3 or 4 nausea, compared to Gemcitabine in combination with cisplatin. Pemetrexed in combination with either Cisplatin or Carboplatin is therefore an appropriate control arm treatment in this phase III trial.

This patient population with a major unmet medical need is therefore appropriate to evaluate the efficacy and safety of AZD9291 in this study.

The study design has been discussed with the US Food and Drug Administration (FDA), Swedish Medical Products Agency (MPA) and French Agence Nationale de Securite du Medicaments (ANSM) during Scientific Advice consultations and all key aspects of the Phase III 2nd line study design including Progression Free Survival (PFS) as primary endpoint, dose rationale and patient population were supported.

Given the unmet medical need that exists in the aforementioned patient population alongside the lack of well-proven treatment options, and given the good evidence of efficacy with AZD9291 (>50% RR in T790M+ population) and well tolerated profile reported in ongoing phase I study in T790M+ patient population (Ranson et al WCLC 2013), it is considered appropriate to assess efficacy and safety of AZD9291 in a randomised open-label phase III study in 2nd line NSCLC versus pemetrexed in combination with cisplatin or carboplatin.

Once 410 subjects have been randomized globally, recruitment will continue only in mainland China until approximately 50 Chinese subjects have been randomized. This is to ensure adequate Chinese subject participation to satisfy China Regulatory Authority requirements; it is anticipated that this target may not be met before the global recruitment of 410 is achieved.

The primary objective of this study is PFS. This is an appropriate primary efficacy endpoint in this NSCLC population and may be associated with an improvement in OS, delay to time of initiation of subsequent therapies, symptom control, and quality of life. Secondary efficacy endpoints are those that are appropriate to this patient population and include, Duration of response (DoR), Disease Control Rate (DCR) [DCR: Complete response (CR) + Partial Response (PR) + Stable disease (SD)] and overall survival. Characterisation of

pharmacokinetics (PK) as well as the safety and tolerability of AZD9291 will also be assessed as a secondary endpoint.

Several exploratory endpoints will be evaluated (see Section 2.4). These include assessment of the effect of AZD9291 compared with chemotherapy on post progression outcomes such as time from randomization to second progression and time to subsequent treatments. Additional exploratory endpoints will include comparisons of AZD9291 with chemotherapy on health state utility (using EQ-5D-5L health state utility index) and resource utilization (e.g. hospital visits), patient self-reporting of adverse events, the relationship between PK and selected endpoints, tumour samples and biomarkers (ctDNA for the assessment of biomarkers) and tumour biopsy for companion diagnostic development.

The collection of cerebrospinal fluid (CSF) from a select number of subjects who provide voluntary optional consent will enable the investigation of the ability of AZD9291, AZ5104 and AZ7550 to cross the blood brain barrier. Brain metastases occur in 20-30% of patients with advanced NSCLC, and are associated with poor prognosis (Porta et al 2011). 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 suggests that AZD9291 may be capable of crossing the blood brain barrier (see Investigator Brochure) and potentially may offer better exposures in this anatomically protected location.

Overall, the totality of primary, secondary and exploratory endpoints in this study will allow a robust characterisation of overall benefit / risk of AZD9291 for patients with metastatic, EGFR T790M+ mutation-positive, non-small cell lung cancer (NSCLC) whose NSCLC has progressed during treatment with an FDA-approved, EGFR tyrosine kinase inhibitor.

The dose of 80 mg once daily was selected from a review of all available safety, tolerability, PK and efficacy data from study D5160C00001, in patients with advanced NSCLC who have progressed following prior therapy with a prior EGFR TKI agent. At the Investigator Brochure (IB) data cut-off of 19 November 2013, AZD9291 had been administered as a capsule formulation across the dose range of 20 to 240mg once daily in this study: 20 mg (n=21), 40 mg (n=55), 80 mg (n=47), 160 mg (n=40) and 240 mg (n=7). No dose limiting toxicities (DLTs) have been reported at any dose level in the escalation cohorts during the 21-day DLT evaluation period. Subjects have once daily doses of AZD9291 for durations of at least 10 months depending on the dose level. Emerging efficacy data has demonstrated durable objective responses from the starting dose level of 20 mg once daily (Ranson et al WCLC 2013). The selected 80 mg dose is four 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 80 mg dose level is considered to have a safety and tolerability profile appropriate for chronic administration to subjects with advanced NSCLC.

Up to the primary PFS analysis, once subjects on the platinum-based doublet chemotherapy arm are determined to have objective radiological progression according to RECIST 1.1 by the investigator and confirmed by independent central imaging review, they will be given the opportunity to begin treatment with AZD9291 80mg, once daily. These subjects may

continue treatment with AZD9291 as long as they show clinical benefit, as judged by the investigator. If a subject has been deemed to have objective disease progression according to Investigator tumour assessment by RECIST 1.1, but is not confirmed by independent central imaging review, he/she is not eligible to cross-over to AZD9291 at that time. Should it be in the subject's best interest, and only if further randomized chemotherapy is warranted, he/she may continue to receive randomized doublet chemotherapy (if initial doublet chemotherapy treatment has not yet been completed) or pemetrexed maintenance monotherapy. Sites are to submit the next scheduled tumour assessment for central imaging review according to Table 2.

Following the primary PFS analysis subjects still on the platinum-based doublet chemotherapy arm will be given the opportunity to begin treatment with AZD9291 80 mg, once daily if it is considered by the Investigator to be in the patient's best interest, and if they are eligible to receive AZD9291 (no contraindications). At least a 14 day washout period is required between last dose of chemotherapy and starting AZD9291 treatment.

If subjects are not eligible to receive AZD9291, they will enter into the follow-up phase of the study, and other treatment options should be discussed by the investigator.

1.4 Benefit/risk and ethical assessment

In the advanced NSCLC post-EGFR TKI treatment failure setting that has been chosen for initial study with AZD9291, median survival is modest (~16 months for second line therapy, ~10 months for third line therapy) with no effective treatment options currently available. This population therefore represents a major unmet medical need. 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 target for the treatment of EGFR T790M mutation-positive NSCLC tumours driven. Specifically the safety profile of AZD9291 is (in the ongoing phase I trial) modest with the majority of adverse events being non-clinically significant EGFR-related adverse events ie, 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 interstitial lung disease as this is an uncommon but well documented EGFR related toxicity. All patients will be assessed for possible known EGFR-related toxicities and detailed information on the management of EGFR-related gastrointestinal, dermatological and ophthalmic is being provided for all AZD9291 studies.

It is therefore reasonable and appropriate to evaluate the oral administration of AZD9291 in comparison to standard platinum-based doublet chemotherapy as a second-line therapy in this unmet medical need post-EGFR TKI EGFR T790M mutation-positive NSCLC patient population, according to the proposed study design.

1.5 Study Design

This is a phase III, open label, randomized study to assess the safety and efficacy of AZD9291 (80 mg, orally, once daily) versus platinum-based doublet chemotherapy in second-line patients with EGFR T790M mutation-positive, locally advanced or metastatic NSCLC, who have progressed following treatment with an approved epidermal growth factor tyrosine kinase inhibitor agent.

Subjects will have to provide a mandatory biopsy sample for central testing of T790M mutation status following confirmed disease progression on the most recent treatment regimen. The T790M mutation status of the subject's tumour must be determined by a designated central laboratory using the cobas® EGFR Mutation Test (Roche Molecular Systems).

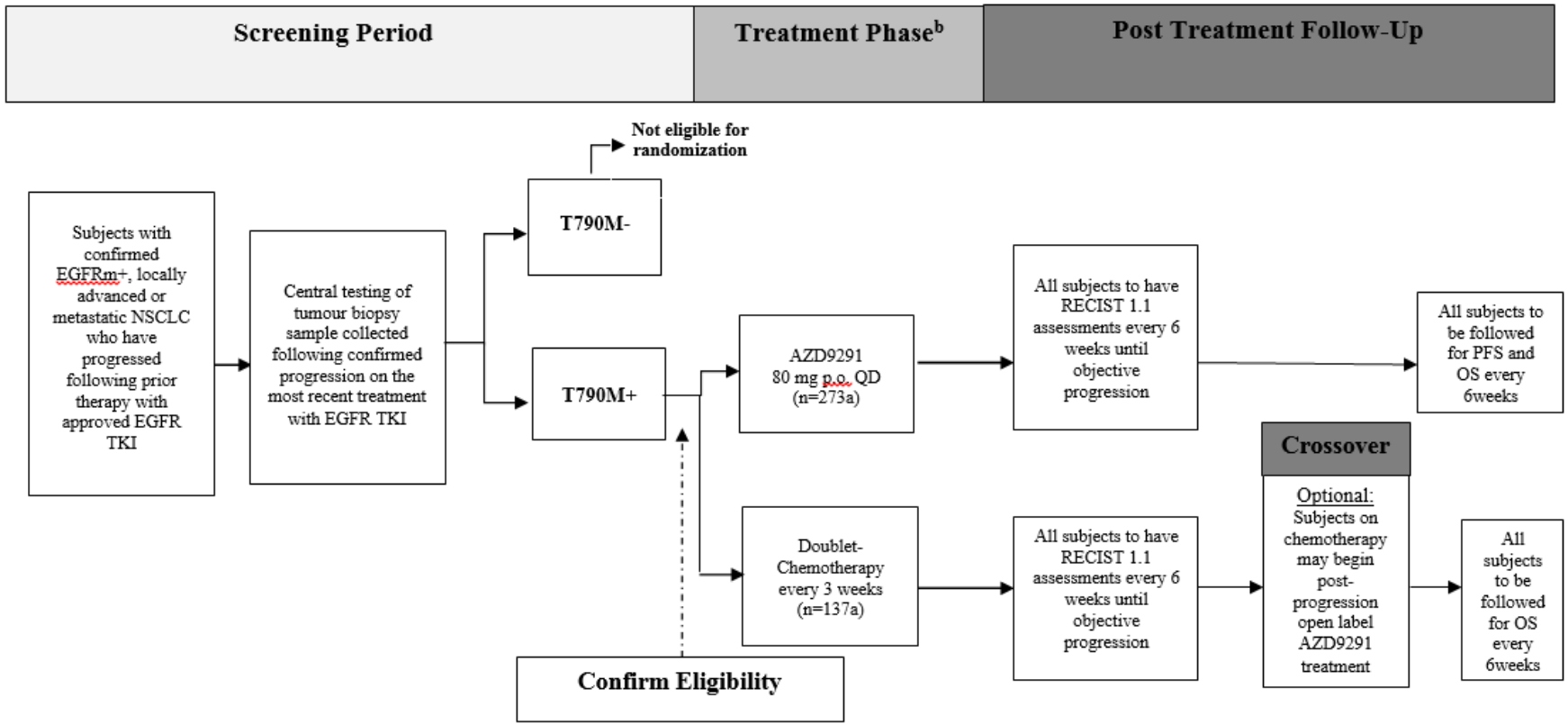
Up to primary PFS analysis, subjects should continue on study treatment until Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) defined progression or until a treatment discontinuation criterion is met. There is no maximum duration of treatment as subjects may continue to receive randomized treatment beyond RECIST 1.1 defined progression as long as they show clinical benefit, as judged by the investigator. Following the primary PFS analysis no further RECIST data will be collected (apart from patients in China. For the China cohort, RECIST data will be collected for China PFS analysis when at least 20 PFS events have been observed out of approximately 50 Chinese subjects).

Once subjects on the platinum-based doublet chemotherapy arm are determined to have objective radiological progression according to RECIST 1.1 by the investigator and confirmed by independent central imaging review, they will be given the opportunity to begin treatment with AZD9291 80 mg, once daily. These subjects may continue treatment with AZD9291 as long as they show clinical benefit, as judged by the investigator.

If a subject has been deemed to have objective disease progression according to Investigator tumour assessment by RECIST 1.1, but is not confirmed by independent central imaging review, he/she is not eligible to cross-over to AZD9291 at that time. Should it be in the subject's best interest, and only if further randomized chemotherapy is warranted, he/she may continue to receive randomized doublet chemotherapy (if initial doublet chemotherapy treatment has not yet been completed) or pemetrexed maintenance monotherapy. Sites are to submit the next scheduled tumour assessment for central imaging review according to Table 2.

Following the primary PFS analysis, subjects still on the platinum-based doublet chemotherapy arm will be given the opportunity to begin treatment with AZD9291 80 mg, once daily if it is considered by the Investigator to be in the patient's best interest, and if they are eligible to receive AZD9291 (no contraindications). At least a 14 day washout period is required between last dose of chemotherapy and starting AZD9291 treatment.

Figure 1 Study flow chart up to primary PFS Analysis



(a) Approximately 410 subjects will be randomized into the trial; from these approximately 273 subjects will be treated with AZD9291 and approximately 137 subjects will be treated with a platinum based doublet-chemotherapy.
(b) Subjects will be considered in "Treatment phase" at the time AZD9291/Doublet-Chemotherapy (study treatment) is started. Subjects will continue to receive study treatment until objective disease progression (according to RECIST 1.1). Subjects randomized to AZD9291 may continue to receive AZD9291 as long as they are continuing to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria. Subjects randomized to the platinum-based doublet chemotherapy arm with objective radiological progression according to RECIST 1.1 by the investigator and confirmed by independent central imaging review will be given the opportunity to begin treatment with AZD9291, 80 mg once daily.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of AZD9291 compared with platinum-based doublet chemotherapy by assessment of Progression Free Survival (PFS).	PFS using investigator assessments according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1). Sensitivity analysis of PFS using Blinded Independent Central Review (BICR).

2.2 Secondary objectives

Secondary Objective:	Outcome Measure :
To further assess the efficacy of AZD9291 compared with platinum-based doublet chemotherapy in terms of: - Objective Response Rate (ORR) - Duration of Response (DoR) - Disease Control Rate (DCR) - Tumour shrinkage - Overall Survival (OS)	ORR, DoR, DCR and tumour shrinkage using investigator assessments according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1). Analysis of overall survival.
To assess the effect of AZD9291 compared to platinum-based doublet chemotherapy on subjects' disease-related symptoms and health related quality of life (HRQoL).	EORTC QLQ-C30 and EORTC QLQ-LC13. EORTC QLQ-C30: Questionnaire consisting of 30 items measuring subjects general cancer symptoms and functioning. EORTC QLQ-LC13: A complementary questionnaire measuring lung cancer symptoms.
To characterise the pharmacokinetics (PK) of AZD9291 and metabolites in subjects receiving AZD9291.	PK exposure parameters derived from plasma concentrations of AZD9291, and metabolites AZ5104 and AZ7550. PK Parameters (CLss/F, Css, min and Css, max AUCss) will be derived using population PK analysis and reported separately to the CSR. Data from this study may form part of a pooled analysis with data from other studies

2.3 Safety objectives

Safety Objective:	Outcome Measure :
To assess the safety and tolerability profile of AZD9291 compared with platinum-based doublet chemotherapy.	Adverse events (graded by CTCAE v4) - Clinical chemistry, haematology and urinalysis - Vital signs (pulse and BP), Physical Examination, Weight - Central Digital ECG - Echocardiogram/MUGA (for LVEF) - WHO performance status)

2.4 Exploratory objectives

Results from such analyses outlined below may be reported separately from the Clinical Study Report (CSR).

Exploratory Objective:	Outcome Measure :
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 subjects treated with AZD9291. Results from such analyses will be reported separately from the Clinical Study Report (CSR). Data from this study may also form part of a pooled analysis with other AZD9291 studies.
To compare the effects of AZD9291 compared with platinum-based chemotherapy on post progression outcomes	Time from randomization to second progression (PFS2) Time to subsequent treatments Time to change in symptoms (including post progression assessments)
To further characterise the effects of AZD9291 on survival outcomes.	Assess the impact on overall survival of baseline potentially prognostic factors (e.g. tumour stage, performance status, sex, baseline LDH) Assess the impact on overall survival of subsequent treatments and other potential covariates (e.g. changes in performance status)
To compare adverse events by subject self-reporting of specific CTCAE symptoms (where applicable) between AZD9291 and chemotherapy.	Collection of approximately 28 PRO-CTCAE symptoms via an electronic device solution (in countries where language is available).

To compare AZD9291 treatment with platinum-based chemotherapy treatment on health state utility.	The EQ-5D-5L health state utility index will be used to derive health state utility based on subject reported data.
To compare health resource use associated with AZD9291 treatment with platinum-based chemotherapy treatment.	Health resource utilisation measures including hospitalization, outpatient visits, or emergency department visits.
To characterise the pharmacokinetics (PK) of AZD9291 and metabolites in cerebrospinal fluid (CSF).	Concentration of AZD9291, AZ5104 and AZ7550. Ratio of metabolites to AZD9291. Ratio of CSF to plasma concentration. Summaries of PK concentration data.
To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence PK or response to AZD9291, platinum-based doublet chemotherapy (ie, absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers.	Correlation of polymorphisms with variation in PK, PD, safety or response observed in subjects treated with AZD9291 or comparator. Data generated may be reported separately and may also form part of a pooled analysis with other AZD9291 studies.
To collect and store tumour samples and blood-based samples for potential for exploratory research into factors that may influence susceptibility to/development of NSCLC/cancer and/or response to AZD9291(where response is defined broadly to include efficacy, tolerability or safety).	Analysis of key genetic and proteomic markers to include, but not limited to, EGFR mutations, HER2 & CMET expression and/or amplication. Collection of plasma samples to include, but not be limited to, extraction of circulating tumour DNA (ctDNA) for investigation of blood borne biomarkers. The sample may be used to investigate the relationship between PK and blood-borne biomarkers. Samples may be analysed retrospectively. Any biomarker data generated may be reported separately and may also form part of a pooled analysis with other AZD9291 studies.
To collect and store plasma for isolation of ctDNA. Extracted ctDNA will be assessed for the presence of genetic abberations including, but not limited to, EGFR mutations (T790M, L858R, etc). These samples may be shared with a diagnostic partner for development of a ctDNA test for T790M detection.	Retrospective/real-time analysis of EGFR (and other) mutations in ctDNA from all study subjects (mandatory).

To collect and store residual CSF for potential exploratory research of factors that may influence development of NSCLC and/or response to AZD9291 (where response is defined broadly to include efficacy, tolerability or safety).	Collection of CSF for the investigation of PK and/or biomarkers. Samples may be analysed retrospectively.

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

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

3.1 Inclusion criteria

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

1. Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses. *If a subject 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 subject and he/she will not be excluded from other aspects of the study.*
2. Female and male subjects aged at least 18 years. Subjects from Japan aged at least 20 years.
3. Subjects with histologically- or cytologically-documented NSCLC.
4. Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy
5. Evidence of radiological disease progression following 1st line EGFR TKI (ie, 1st line treatment for advanced/metastatic disease) without any further treatment.
6. Subjects must have a diagnosis of "Nonsquamous Non-Small Cell Lung Cancer" in order to be eligible to receive treatment with pemetrexed platinum-based doublet chemotherapy in accordance with local prescribing information.
7. Documented EGFR mutation (at any time since the initial diagnosis of NSCLC) known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q).
8. Subjects must have central confirmation of tumour T790M+ mutation status from a tissue biopsy sample taken after documented disease progression on first line treatment with an approved, EGFR tyrosine kinase inhibitor.
9. WHO performance status 0-1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks.
10. 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 ≥ 10mm in the longest

diameter (except lymph nodes which must have short axis ≥ 15mm) with computerised tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements. If only one measurable lesion exists, it is acceptable to be used 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.

11. Females should be using adequate contraceptive measures, should not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:
    - Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
    - Women under 50 years old would be considered 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.
12. Male subjects should be willing to use barrier contraception ie, condoms.
13. For inclusion in **optional genetic research**, subject must provide informed consent for genetic research.

    If a subject 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 subject and he/she will not be excluded from other aspects of the study.

3.2 Exclusion criteria

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

1. Treatment with any of the following:
    - Treatment with more than one prior line of treatment for advanced NSCLC
    - Treatment with an EGFR-TKI (e.g., erlotinib, gefitinib or afatinib) within 8 days or approximately 5x half-life, whichever is the longer, of the first dose of study treatment. (If sufficient washout time has not occurred due to schedule or PK properties, an alternative appropriate washout time based on known duration and time to reversibility of drug related adverse events could be agreed upon by AstraZeneca and the Investigator)
    - Any investigational agents or other anticancer drugs from a previous treatment regimen or clinical study within 14 days of randomization

- Previous treatment with AZD9291, or a 3rd generation EGFR TKI
- Prior neo-adjuvant or adjuvant chemotherapy treatment within 6 months of starting 1st EGFR TKI treatment
- Major surgery (excluding placement of vascular access) within 4 weeks of randomization
- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of randomization
- Subjects currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of AZD9291) medications or herbal supplements known to be potent inhibitors or inducers of CYP3A4 (Appendix E)
- Treatment with an investigational drug within five half-lives of the compound

2. Any unresolved toxicities from prior therapy greater than CTCAE grade 1 (with the exception of alopecia grade 2) at the time of starting study treatment.

3. Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 4 weeks prior to start of study treatment.

4. 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 subject 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). Screening for chronic conditions is not required.

5. 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.

6. Any of the following cardiac criteria:

   - Mean resting corrected QT interval (QTc) > 470 msec, obtained from 3 electrocardiograms (ECGs)
   - 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 >250msec
   - 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.

7. Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.

8. 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) > 2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or > 5 times ULN in the presence of liver metastases
   - Aspartate aminotransferase (AST) > 2.5 times ULN if no demonstrable liver metastases or > 5 times ULN in the presence of liver metastases
   - Total bilirubin > 1.5 times ULN if no liver metastases or > 3 times ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or liver metastases
   - Creatinine >1.5 times ULN 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 > 1.5 times ULN.

9. History of hypersensitivity of AZD9291 (or drugs with a similar chemical structure or class to AZD9291) or carboplatin or pemetrexed or cisplatin, or any exipients of these agents.

10. Women who are breast-feeding.

11. Males and females of reproductive potential who are not using and effective method of birth control and females who are pregnant or breastfeeding or have a positive (urine or serum) pregnancy test prior to study entry.

12. Contraindication for pemetrexed and cisplatin/carboplatin (e.g. predominantly squamous cell histology).

13. Involvement in the planning and conduct of the study (applies to AstraZeneca staff or staff at the study site).

14. Judgment by the investigator that the subject should not participate in the study if the subject is unlikely to comply with study procedures, restrictions and requirements.

In addition, the following is considered a criterion for exclusion from the exploratory genetic research:

15. Previous allogenic bone marrow transplant.

16. Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

Procedures for withdrawal of incorrectly randomized subjects see Section 3.4.

3.3 Subject screening and randomization

Investigator(s) should keep a subject pre-screening log of subjects considered for the study.

The Investigator(s) will:

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

2. Determine subject eligibility. See Section 3.1 and 3.2.

3. 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 ECCNN**3**XX: CC being the country code, NN being the centre number and 3XX being the subject enrolment code at the centre into AURA3 study.

At Visit 2, once the subject is deemed eligible, the Principal Investigator or suitably trained delegate will:

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

Randomization codes will be assigned as subjects become eligible for randomization.

If a subject is re-screened, always a new E-code will be assigned. Any repeated tests and/or procedures will be performed as per documented local standards. Subjects will reconfirm their consent to participate in the study by resigning and dating their original consent form(s), next to their initial signature and date. A subject with a valid negative T790M result cannot be re-screened.

The following assessments need to be repeated for subjects who are re-screened and where >28 days will have lapsed since their last screening period to the date of proposed randomization:

- Demography & baseline characteristics
- Medical/surgical history
- Inclusion/exclusion criteria
- Physical examination, including weight
- WHO performance status

- Pregnancy test (if applicable)
- Vital signs (pulse and BP)
- Clinical chemistry/haematology/urinalysis
- Digital ECG
- Echocardiogram/MUGA (if clinically needed)
- Tumour assessments (RECIST 1.1)
- Concomitant medications & procedures
- Adverse events
- Anti-cancer treatment

A subject randomized to platinum-based doublet chemotherapy who crosses over to AZD9291 will be managed via IVRS/IWRS.

If a subject withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused.

Note: Section 4.1 describes the procedures to be carried out during screening/enrolment period. Section 4.2 describes procedures to be carried out during randomization period.

3.4 Procedures for handling incorrectly randomized subjects

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

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

3.5 Methods for assigning treatment groups

Suitable subjects will be centrally randomized to receive either AZD9291 80mg QD p.o. or platinum-based doublet chemotherapy (pemetrexed 500mg/m^2 + carboplatin AUC5 or pemetrexed 500mg/m^2 + cisplatin 75mg/m^2) on Day 1 of every 21d cycle in a 2:1 (AZD9291: platinum-based doublet chemotherapy) ratio using the IVRS/IWRS system. The investigational site must declare (in IVRS/IWRS), prior to randomization, their choice of chemotherapy for that subject.

Subjects will be stratified at randomization based on ethnicity (Asian/Non-Asian).

Investigators will have the option to provide AZD9291 80mg, once daily, to subjects randomized to platinum-based doublet chemotherapy, who are determined by them to have objective radiological progression according to RECIST 1.1, and who have objective disease progression confirmed by the independent central imaging review.

3.6 Restrictions

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

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

2. Male subjects should be asked to use barrier contraceptives (ie, by use of condoms) during sex with all partners during the trial and for a washout period of 4 months. Subjects should avoid procreation for 6 months after completion of trial treatment. Subjects should refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment. If male subjects wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment. For subjects receiving platinum-based doublet chemotherapy, above recommendations should be in accordance with the local prescribing label.

3. Once enrolled, all subjects must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known potent inducers of CYP3A4 whenever feasible, but subjects may receive any medication that is clinically indicated for treatment of adverse events. 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 eCRF. Guidance on medicines to avoid, medications that require close monitoring and on washout periods is provided (see Appendix E).

4. If medically feasible, subjects taking regular medication, with the exception of potent inducers of CYP3A4 (see above), should be maintained on it throughout the study period. Subjects randomized to AZD9291 taking concomitant medications whose disposition is dependent upon Breast cancer resistance protein (BCRP) and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication

whilst receiving AZD9291. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Appendix E).

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

Subjects taking warfarin should be monitored regularly for changes in prothrombin time or international normalized ratio (INR).

5. Subjects who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE grade ≤2) while receiving treatment with AZD9291 until at least one week after symptoms have resolved. If a subject has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events they must discontinue wearing their contact lenses until at least one week after treatment with AZD9291 is permanently discontinued. Subjects must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by a study doctor, at any time during the study until 1 week after AZD9291 has been permanently discontinued. Subject should consult the clinic promptly if they have any concerns.

3.7 Discontinuation from study treatment

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

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Pregnancy
- Severe non-compliance with the study protocol as judged by the investigator and/or AstraZeneca
- Subject incorrectly initiated on study treatment
- Objective disease progression or subject is no longer receiving clinical benefit
- Lost to follow up.

3.7.1 Procedures for discontinuation of a subject from study treatment

The Principal Investigator/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 subject. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up (See Section 6); electronic questionnaire devices (e.g., for

patient reported outcomes) and all unused study drug should be returned by the subject or representative (e.g. caretaker, family member).

Any subject who discontinues study treatment for reasons other than objective disease progression should have tumour assessments performed as scheduled in the protocol (see Table 1 or Table 2) until objective disease progression is documented or death occurs, unless consent is withdrawn. (Note: following the primary PFS analysis tumour assessments will no longer be collected apart from patients in China. For the China cohort, RECIST data will be collected for China PFS analysis when at least 20 PFS events have been observed out of approximately 50 Chinese subjects. Following China PFS analysis, tumour assessments will no longer be collected for China cohort). Study procedures related to PROs, SAEs and anti-cancer treatment must be captured until permanent withdrawal from the study.

If a subject is withdrawn from study, see Section 3.8.

3.8 Criteria for withdrawal

At any time, subjects are free to discontinue study treatment or withdraw from the study (ie, study treatment and assessments), without prejudice to further treatment. A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 6); electronic questionnaire devices (ePRO) and all investigational products should be returned by the subject or representative. The term withdrawal from the study refers to both discontinuation from study treatment and study assessments.

Reasons for withdrawal from the study:

- Eligibility criteria not fulfilled
- Death
- Withdrawal of consent.

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

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

Withdrawn subjects will not be replaced.

3.8.1 Screen/enrolment failures

Screen/enrolment failures are subjects who do not fulfil the eligibility criteria for the study, and therefore must not receive AZD9291. These subjects should have the reason for study withdrawal recorded as "Eligibility Criteria not fulfilled" (ie, subject does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen/enrolment failures (not subjects who have received investigational product).

3.8.2 Withdrawal of the informed consent

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

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. The subject or representative will return the ePRO device and unused AZD9291 tablets.

If a subject withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused.

3.9 Termination of the study

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

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

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

In the case of terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subject's interest.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan for AZD9291 Subjects up to Primary PFS Analysis

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles as per Cycle 7)								Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+	Treatment Discontinuation	28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day		C1 *D1*	C1 *D8*	C1 *D15*	C2 D1	C3 D1	C4-6 D1	C7[b]+ D1	NA	NA	NA	NA	
Day	-28 to 1	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)[y]	NA	0	±2	±2	±7	±7	±7	±7	0	+7	± 7	± 7	**SECTION:**
Informed consent[c]	X												3.3, 4.1, 4.2, 4.3
Submit tumour tissue sample for mutation analysis[d]	X												4.1 & 5.6
Collect/submit optional tumour biopsy for exploratory research & diagnostic development	X								X[u]		X[u]		4.1 & 5.6
Archival tumour tissue[e]	X												5.6
Demography & baseline characteristics	X												4.1
Medical/surgical history	X												4.1
Inclusion/exclusion criteria	X												3
Physical examination, including weight[m]	X	X[f]			X	X	X	X	X	X[w]			5.2.3, 5.2.6.1

Table 1 Study Plan for AZD9291 Subjects up to Primary PFS Analysis

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles as per Cycle 7)							Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day		C1 *D1*	C1 *D8*	C1 *D15*	C2 D1	C3 D1	C4-6 D1	C7[b]+ D1	NA	NA	NA	NA	
Day	-28 to 1	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)[y]	NA	0	±2	±2	±7	±7	±7	±7	0	+7	± 7	± 7	SECTION:
Height	X												5.2.6.1
WHO Performance status[m]	X	X			X	X	X	X	X		X	X	4.1
Pregnancy test (pre-menaopausal females only)	X												5.2.1
Ophthalmologic assessment	X	← as clinically indicated →											5.2.7.1
Plasma sample for ctDNA[m] and blood borne biomarkers	X[h]	X	X	X	X	X	X	← every 6 weeks in line with RECIST assessments[i] →					5.6.2
Vital signs (pulse and BP)[m]	X	X	X	X	X	X	X	X	X	X[w]			5.2.6
Clinical chemistry/ Haematology/Urinalysis[m]	X	X	X	X	X	X	X	X	X	X[w]			5.2.1
PK blood sample (including metabolites)		X				X	X C5 only	X[v]					5.4
Digital ECG[g]	X	X	X	X	X	X	X	X	X	X[w]			5.2.4
Echocardiogram/MUGA (for LVEF)	X		← every 12 weeks (± 1 week) relative to randomization →							X[w]			5.2.5
Optional genetic consent and sample	X[j]												5.5

Table 1 Study Plan for AZD9291 Subjects up to Primary PFS Analysis

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles as per Cycle 7)								Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+	Treatment Discontinuation	28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day		C1 *D1*	C1 *D8*	C1 *D15*	C2 D1	C3 D1	C4-6 D1	C7[b]+ D1	NA	NA	NA	NA	
Day	-28 to 1	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)[y]	NA	0	±2	±2	±7	±7	±7	±7	0	+7	± 7	± 7	SECTION:
Optional CSF sample					X (once only)[k]								5.4.4
Tumour assessments[l] (RECIST v1.1)	X	every 6 weeks (± 1 week) relative to randomization until disease progression											4.1, 4.2, 4.3.3, 5.1.1, 5.1.2
EORTC QLQ-C30 and EQ-5D-5L (by e-device)[x]		X[m]	every 6 weeks (± 1 week) relative to randomization						X		X[n]	X[n]	5.3.2
EORTC QLQ LC13 (by e-device)[x]		X[m]	weekly (± 2 days) relative to randomization		every 3 weeks (± 3 days) relative to randomization				X		X[o]	X[o]	5.3.2
PRO-CTCAE (by e-device)[p, x]		X[m]	weekly (± 2 days) for first 18 weeks from randomization					X[q]	X		X[o]	X[o]	5.3.2
Healthcare Resource Use		asked for at every visit											5.3.2.5
IVRS/IWRS	X	X			X	X	X	X[b]	X				3.3, 3.5
Dispense study medication		X			X	X	X	X[b]					3.3
Dose with AZD9291		Daily dosing											7.1
Concomitant medication & procedures													7.7
Adverse events											X[r]		6.3 & 6.4

Table 1 Study Plan for AZD9291 Subjects up to Primary PFS Analysis

Visit	Screening/ Enrolment	Treatment Period (further treatment cycles as per Cycle 7)								Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+	Treatment Discontinuation	28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day		C1 *D1*	C1 *D8*	C1 *D15*	C2 D1	C3 D1	C4-6 D1	C7[b]+ D1	NA	NA	NA	NA	
Day	-28 to 1	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)[y]	NA	0	±2	±2	±7	±7	±7	±7	0	+7	± 7	± 7	SECTION:
Survival Status												X[s]	4.3.4
Anti-cancer treatment	X										X	X[s]	4.2
Subsequent response/ progression data												X[t]	5.8

a A cycle is defined as 21-day treatment period.

b Visit schedule changes after Cycle 7 Day 1 from every 21 days (3 weeks) to every 42 days (6 weeks).

c Consent may be taken prior to the 28-day window if required. The screening period will then start with first study-related assessment, excluding the collection of the tumour tissue sample for central mutation analysis.

d Taken following progression on the latest line of therapy. The collection of this tumour tissue sample for central mutation analysis is not included in the 28-day screening period.

e Archival tumour sample only to be submitted after T790M positive status confirmed by central testing. Not required for T790M negative patients.

f If assessments are not done at Visit 2, but have been done at Visit 1 and within 14 day window prior to staring study treatment, with no change in condition and no clinical indication to do so, they do not have to be repeated on Visit 2 (except for fasting glucose).

g There is a potential to move from centrally reviewed to locally reviewed ECGs upon review of QT data of approximately 100 subjects.

h To be taken prior to receiving the central T790M mutation result. All screening plasma samples are required by AstraZeneca, regardless of the outcome of the mutation screening.

i Collect every 6 weeks up to and including progression (corresponding with the RECIST assessments – and continuing after treatment discontinuation in absence of disease progression). If patient discontinues from study, please collect a sample at treatment discontinuation and at Progression follow-up.

j If for any reason the sample is not drawn prior to randomization it may be taken at any visit until the last study visit.

k To be obtained at one time point at any time from Cycle 2 Day 1 onwards.

l At least one lesion, not previously irradiated that can be accurately measured.

m To be completed pre-dose.

n Assess every 6 weeks (± 1 week) relative to the date of randomization until end of study (including survival follow-up period) and at the time of progression.

o Assess every 3 weeks (± 3 days) relative to the date of randomization until end of study (including survival follow-up period) and at the time of progression.

p PRO-CTCAE will only be administered in those languages where a linguistically validated version exists.

q Assessed at Cycle 7 Day 1 then every 3 weeks (± 3 days) relative to the date of randomization thereafter until end of study (including survival follow-up period) and at the time of progression.

r Following AZD9291 discontinuation, SAEs considered related to study procedures should continue to be collected until disease progression.

s 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.]

t Record subsequent response/progression data every 6 weeks until first confirmed disease progression on a subsequent treatment.

u Discontinuation biopsy can be taken at discontinuation or progression, whichever comes first.

v After Cycle 7, every other cycle up to and including Cycle 13.

w A 28-day follow-up assessment will be required if on treatment assessment was abnormal at treatment discontinuation.

x ePRO LogPads must be assigned to subjects only on the day of randomization; baseline ePROs should be completed by subjects prior to dosing, when they are still in the clinic on the day of randomization, to ensure these are done properly.

y Visit windows are always calculated in relation to Cycle 1, Day 1.

Table 2 Study Plan for Platinum-based Doublet-Chemotherapy Subjects up to Primary PFS Analysis

Visit	Screening/ Enrolment	Randomization	Treatment Period (further treatment cycles as per Cycle 7)							Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	1	2		3	4	5	6	7-9	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day			C1 *D1*[f]	C1 *D8*	C1 *D15*	C2 D1	C3 D1	C4-6 D1	C7[b] +	NA	NA	NA	NA	
Day	-28 to 1	-7 to 1	1	8	15	22	43	64-106	127 +	NA	NA	NA	NA	
Window (days)[y]	NA	-7	0	±2	±2	±7	±7	±7	±7	0	+7	± 7	± 7	SECTION:
Informed consent[c]	X													3.3, 4.1, 4.2, 4.3
Submit tumour tissue sample for mutation analysis[d]	X													4.1 & 5.6
Collect and submit optional tumour biopsy for exploratory research and diagnostic development	X									X[u]		X[u]		4.1 & 5.6
Archival tumour tissue[e]	X													5.6
Demography & baseline characteristics	X													4.1
Medical/surgical history	X													4.1
Inclusion/exclusion criteria	X													3

Table 2 Study Plan for Platinum-based Doublet-Chemotherapy Subjects up to Primary PFS Analysis

Visit	Screening/ Enrolment	Randomization	Treatment Period (further treatment cycles as per Cycle 7)						Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day			C1 *D1*[f]	C1 *D8*	C1 *D15*	C2 D1	C3 D1	C4-6 D1	C7[b] +	NA	NA	NA	NA	
Day	-28 to 1	-7 to 1	1	8	15	22	43	64-106	127 +	NA	NA	NA	NA	
Window (days)[y]	NA	-7	0	±2	±2	±7	±7	±7	±7	0	+7	± 7	± 7	SECTION:
Physical examination, including weight[m]	X	X[g]			X	X	X	X[v]	X	X[v]				5.2.3, 5.2.6.1
Height	X													5.2.6.1
WHO Performance status[m]	X	X			X	X	X	X	X		X	X		4.1
Pregnancy test (pre-menaopausal females only)	X													5.2.1
Ophthalmologic assessment	X		← as clinically indicated →											5.2.7.1
Vital signs (pulse and BP)[m]	X		X	X	X	X	X	X	X	X	X[v]			5.2.6
Clinical chemistry/ Haematology/ Urinalysis[m]	X	X[g]		X	X	X	X	X	X[v]	X	X[v]			5.2.1

Table 2 Study Plan for Platinum-based Doublet-Chemotherapy Subjects up to Primary PFS Analysis

Visit	Screening/ Enrolment	Randomization	Treatment Period (further treatment cycles as per Cycle 7)						Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day			C1 *D1*[f]	C1 *D8*	C1 *D15*	C2 D1	C3 D1	C4-6 D1	C7[b] +	NA	NA	NA	NA	
Day	-28 to 1	-7 to 1	1	8	15	22	43	64-106	127 +	NA	NA	NA	NA	
Window (days)[y]	NA	-7	0	±2	±2	±7	±7	±7	±7	0	+7	± 7	± 7	**SECTION:**
Plasma sample for ctDNA[m] and blood borne biomarkers	X[h]	X	X	X	X	X	X	every 6 weeks in line with RECIST assessments						5.6.2
Digital ECG[k]	X	X	X	X	X	X	X	X[v]	X	X[v]				5.2.4
Echocardiogram/MUGA (for LVEF)	X		every 12 weeks (± 1 week) relative to randomization							X[v]				5.2.5
Optional genetic consent and sample	X[j]													5.5
Tumour assessments (RECIST v1.1)[l]	X		every 6 weeks (± 1 week) relative to randomization until disease progression											4.1, 4.2, 4.3.3, 5.1.1, 5.1.2
EORTC QLQ-C30 and EQ-5D-5L (by e-device)[w]		X	every 6 weeks (± 1 week) relative to randomization						X		X[n]	X[n]		5.3.2
EORTC QLQ LC13 (by e-device)[w]		X	weekly(± 2 days) relative to randomization			every 3 weeks (± 3 days) relative to randomization			X		X[o]	X[o]		5.3.2
PRO-CTCAE (by e-device)[p, w]		X	weekly (± 2 days) for first 18 weeks from randomization					X[q]	X		X[o]	X[o]		5.3.2

Table 2 Study Plan for Platinum-based Doublet-Chemotherapy Subjects up to Primary PFS Analysis

Visit	Screening/ Enrolment	Randomization	Treatment Period (further treatment cycles as per Cycle 7)							Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	1	2		3	4	5	6	7-9	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day			C1 *D1*[f]	C1 *D8*	C1 *D15*	C2 D1	C3 D1	C4-6 D1	C7[b] +	NA	NA	NA	NA	
Day	-28 to 1	-7 to 1	1	8	15	22	43	64-106	127 +	NA	NA	NA	NA	
Window (days)[y]	NA	-7	0	±2	±2	±7	±7	±7	±7	0	+7	± 7	± 7	SECTION:
Healthcare Resource Use			← asked for at every visit →											5.3.2.5
IVRS/IWRS	X	X								X				3.3, 3.5, 7.2
Folic Acid administration (pre-treatment)		← 5-7d prior to 1st infusion; daily during treatment period →												4.2
Vitamin B12 (pre-treatment)		← Within 7d prior to 1st infusion; every 9 weeks during treatment period →												4.2
Corticosteroid administration (pre-treatment)		← On the day prior to, on the day, and on the day after infusion →												4.2
Platinum-based Doublet Chemotherapy[x]			X			X	X	X						3.3, 7.2
Concomitant medication & procedures	←								→					7.7
Adverse events	←								→			X[r]		6.3 & 6.4

Table 2 Study Plan for Platinum-based Doublet-Chemotherapy Subjects up to Primary PFS Analysis

Visit	Screening/ Enrolment	Randomization	Treatment Period (further treatment cycles as per Cycle 7)							Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+	Treatment Discontinuation	28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day			C1 *D1*[f]	C1 *D8*	C1 *D15*	C2 D1	C3 D1	C4-6 D1	C7[b] +	NA	NA	NA	NA	
Day	-28 to 1	-7 to 1	1	8	15	22	43	64-106	127 +	NA	NA	NA	NA	
Window (days)[y]	NA	-7	0	±2	±2	±7	±7	±7	±7	0	+7	± 7	± 7	SECTION:
Survival Status													X[s]	4.3.4
Anti-cancer treatment	X											X	X[s]	4.2
Subsequent response/ progression data													X[t]	5.8

a A cycle is defined as 21-day treatment period.

b Visit schedule changes after Cycle 7 Day 1 from every 21 days (3 weeks) to every 42 days (6 weeks). Platinum-based doublet chemotherapy will be administrated every 21 days from previous cycle's day 1. Subjects can continue to receive platinum-based doublet-chemotherapy until meeting discontinuation criteria (see Section 3.9) or up to a total of 6 cycles or until progression (whichever occurs first). Each cycle treatment may be interrupted for a maximum of 21 days. If cycle treatment is delayed by more than 21 days, subject will be permanently discontinued from doublet-chemotherapy. If appropriate, and according to the approved label use or local practice guidelines, pemetrexed may be continued as maintenance treatment. In case of treatment interruption, other assessments are to be done as originally planned. Subjects whose disease has not progressed after four cycles of platinum-based doublet chemotherapy may receive pemetrexed maintenance therapy.

c Consent may be taken prior to the 28-day window if required. The screening period will then start with first study-related assessment, excluding the collection of the tumour tissue sample for central mutation analysis.

d Taken following progression on the latest line of therapy. The collection of this tumour tissue sample for central mutation analysis is not included in the 28-day screening period.

e Archival tumour sample only to be submitted after T790M positive status confirmed by central testing. Not required for T790M negative patients.

f Chemotherapy may start within 1 week after randomization to allow Vitamin B12, Folic acid and corticosteroid treatment, as well as any other assessments for this visit, with the exception of the ePROs, which must be assigned to the subject on the date of randomization.

g If assessments are not done at Visit 2, but have been done at Visit 1 and within 14 day window prior to starting study treatment, with no change in condition and no clinical indication to do so, they do not have to be repeated on Visit 2 (Except for fasting glucose).

h To be taken prior to receiving the central T790M mutation result. All screening plasma sample are required by AstraZeneca, regardless of the outcome of the mutation screening.

i Collect every 6 weeks up to and including progression (corresponding with the RECIST assessments – and continuing after treatment discontinuation in absence of disease progression). If patient discontinues from study, please collect a sample at treatment discontinuation and at Progression follow-up.

j If for any reason the sample is not drawn prior to randomization it may be taken at any visit until the last study visit.

k There is a potential to move from centrally reviewed to locally reviewed ECGs upon review of QT data of approximately 100 subjects.

l At least one lesion, not previously irradiated, that can be accurately measured. Subjects randomized to the platinum-based doublet chemotherapy arm with objective radiological progression according to RECIST 1.1 confirmed by the Investigator and by independent central imaging review will be given the opportunity to cross-over and begin treatment with AZD9291 80mg, once daily. For subjects under consideration for cross-over to AZD9291, scheduled tumour assessments will continue until confirmation of objective radiological disease progression by independent central imaging review**.**

m To be completed pre-dose for all cycles.

n Assess every 6 weeks (± 1 week) relative to the date of randomization until end of study (including survival follow-up period) and at the time of progression.

o Assess every 3 weeks (± 3 days) relative to the date of randomization until end of study (including survival follow-up period) and at the time of progression.

p PRO-CTCAE will only be administered in those languages where a linguistically validated version exists.

q Assessed at Cycle 7 Day 1 then every 3 weeks (± 3 days) relative to the date of randomization thereafter until end of study (including survival follow-up period) and at the time of progression.

r Following chemotherapy discontinuation, SAEs considered related to study procedures should continue to be collected until disease progression.

s Survival status including anti-cancer treatment to be performed every 6 weeks (relative to randomization) following disease progression or withdrawal from treatment. Additional survival calls will be made in the 2 weeks following the date of the data cut-off for each OS analysis.

t Record subsequent response/progression data every 6 weeks until first confirmed disease progression on a subsequent treatment.

u Discontinuation biopsy can be taken at discontinuation or progression, whichever comes first.

v A 28-day follow-up assessment will be required if on treatment assessment was abnormal at treatment discontinuation.

w ePRO LogPads must be assigned to subjects only on the day of randomization; baseline ePROs should be completed prior to dosing, by subjects when they are still in the clinic on the day of randomization, to ensure these are done properly.

x Platinum-based doublet chemotherapy must be administered no less than every 21 days from previous cycle Day 1

y Visit windows are always calculated in relation to Cycle 1 Day 1.

Table 3 Study Plan for Subjects Crossing Over to AZD9291 up to Primary PFS Analysis

Visit	Cross-over AZD9291 Treatment Visit	AZD9291 Treatment Discontinuation	Survival follow-up	For details see Protocol Section
Cycle[a]/ Day	Each cycle	NA	NA	
Day	1	NA	NA	
Window (days)[j]	± 7	0	± 7	SECTION:
Cross-over Informed Consent	X			3.3, 4.1, 4.2, 4.3
Physical examination, including weight [h]	X	X		5.2.3, 5.2.6.1
WHO Performance status [h]	X	X	X	4.1
Vital signs (pulse and BP)[h]	X	X		5.2.6
Clinical chemistry/ Haematology/Urinalysis [h]	X	X		5.2.1
Digital ECG[h]	X	X		5.2.4
EORTC QLQ-C30 and EQ-5D-5L (by e-device)	X[c]	X	X[c]	5.3.2
EORTC QLQ LC13 (by e-device)	X[d]	X	X[d]	5.3.2
PRO-CTCAE (by e-device)[e]	X[d]	X	X[d]	5.3.2
IVRS/IWRS	X	X		3.3, 3.5
Dose with AZD9291[i]	X			7.1
Concomitant medication & procedures	X			6.7
Adverse events	X[f]			6.3 & 6.4
Survival Status			X[g]	4.3.4
Anti-cancer treatment	X		X[g]	4.3

[a] A cycle for subjects crossing over to AZD9291 is defined as 42-day treatment period.

[b] Cross-over consent must be given prior to cross-over from platinum doublet-chemotherapy to AZD9291 treatment.

[c] Assess every 6 weeks (± 1 week) relative to the date of randomization until end of study (including survival follow-up period)

[d] Assess every 3 weeks (± 3 days) relative to the date of randomization until end of study (including survival follow-up period)

[e] PRO-CTCAE will only be administered in those languages where a linguistically validated version exists.

[f] Following platinum-based doublet chemotherapy discontinuation, SAEs considered related to study procedures should continue to be collected until resolution.

[g] Survival status including anti-cancer treatment to be performed every 6 weeks (relative to the date of randomization) following subsequent disease progression with cross-over AZD9291 treatment, 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.]

[h] To be completed pre-dose on each cross-over AZD9291 treatment visit day

[i] AZD9291 will be dispensed every 42 days.

[j] Cross-over visit windows are always calculated in relation to Cycle 1 Day 1 of cross-over AZD9291 treatment.

Table 4 Study Schedule Post Primary PFS Analysis and up to the Final OS Analysis

Visit	Treatment post primary PFS analysis every 84 days (12 weeks)		Follow-up Period			For details see Protocol Section
		Treatment Discontinuation	28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day	C7+ D1	NA	NA	NA	NA	
Window (days)	±7	NA	± 7	± 7	± 7	
Collect and submit optional tumour biopsy for exploratory research and diagnostic development		X[b]		X[b]		4.1 & 5.6
Physical examination, including weight[d]	X	X	X[c]			5.2.3 & 5.2.6.1
WHO Performance status[d]	X	X		X	X	4.1
Pregnancy test (pre-menopausal females only)	as clinically indicated					5.2.1
Ophthalmolgic assessment	as clinically indicated					5.2.7.1
Plasma sample for ctDNA and blood borne biomarkers		X		X[d]		5.6.2
Vital signs (pulse and BP)[d]	X	X	X[c]			5.2.6
Clinical chemistry/ Haematology/Urinalysis[d]	X	X	X[c]			5.2.1
Local ECG assessment[e]	X	X	X[c]			5.2.4
Echocardiogram/MUGA	X		X[c]			5.2.5

Visit	**Treatment post primary PFS analysis every 84 days (12 weeks)**		**Follow-up Period**			**For details see Protocol Section**
		Treatment Discontinuation	**28-day follow-up**	**Progression follow-up**	**Survival follow-up**	
Cycle[a] / Day	**C7+ D1**	**NA**	**NA**	**NA**	**NA**	
Window (days)	**±7**	**NA**	**± 7**	**± 7**	**± 7**	
Optional genetic consent and sample	X[f]					5.5
Optional CSF sample	X (once only)[g]					5.4.4
Tumour assessments	As per routine clinical practice					4.2 & 5.1.1
EORTC QLQ-C30 and EQ-5D-5L (by e-device)[h]	X	X		X	X	5.3.2
EORTC QLQ LC13 (by e-device)[i]	X	X		X	X	5.3.2
PRO-CTCAE (by e-device)[i]	X	X		X	X	5.3.2
IVRS/IWRS	X	X				3.3, 3.5
Dispense study medication	X					3.3
Concomitant medication & procedures	←	→				7.7
Adverse events	←	→		X[j]		6.3 & 6.4
Survival Status					X[k]	4.3.4
Anti-cancer treatment				X	X[k]	4.2
Subsequent response/ progression data					X[lm]	5.8

Visit	**Treatment post primary PFS analysis every 84 days (12 weeks)**		**Follow-up Period**			**For details see Protocol Section**
		Treatment Discontinuation	**28-day follow-up**	**Progression follow-up**	**Survival follow-up**	
Cycle[a]/ Day	**C7+ D1**	**NA**	**NA**	**NA**	**NA**	
Window (days)	**±7**	**NA**	**± 7**	**± 7**	**± 7**	
Healthcare Resource Use[m]	X	X	X			5.3.2.5

a A cycle is defined as 21-day treatment period.
b Discontinuation biopsy can be taken at discontinuation or progression, whichever comes first.
c A 28-day follow-up assessment will be required if on treatment assessment was abnormal at treatment discontinuation.
d To be taken at the time of progression.
e Central ECG is required up to the first OS analysis DCO. Post the first OS analysis DCO, ECGs will be collected locally and stored at the site.
f If for any reason the sample is not drawn prior to randomization it may be taken at any visit until the last study visit.
g To be obtained at one time point at any time from Cycle 2 Day 1 onwards.
h Assess every 6 weeks (± 1 week) relative to the date of randomization until end of study (including survival follow-up period) and at the time of progression.
i Assess every 3 weeks (± 1 week) relative to the date of randomization until end of study (including survival follow-up period) and at the time of progression.
j Following treatment discontinuation, SAEs considered related to study procedures should continue to be collected as outlines in Table 10
k Survival status including anti-cancer treatment to be performed every 6 weeks (relative to randomization) following disease progression or withdrawal from treatment.
[Note: Additional survival calls will be made in the 2 weeks following the date of the data cut-off for each OS analysis.]
l Record subsequent response/progression data every 6 weeks until first confirmed disease progression on a subsequent treatment.
m The information is required up to the first OS analysis DCO. Post the first OS analysis DCO, the information is not to be collected.

4.1 Screening period

It is recommended the screening assessments be performed in a stepwise process beginning with the confirmation of T790M mutation status as determined by the designated central laboratory. However, certain screening assessments must be done in parallel to the T790M mutation assessment, as appropriate (e.g. Baseline ctDNA and blood borne biomarkers plasma samples must be taken before central T790M status result is known). Procedures will be performed according to the Study Plan (Table 1 or Table 2). Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study, provided the assessments fall within the protocol specified period prior to randomization.

At screening, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet these criteria must not be randomized into the study. Demographic data and other characteristics will be recorded and will include date of birth or age, gender, smoking history, race and/or ethnicity according to local regulations.

Subjects will be considered in screening/enrolment period until all Visit 1 assessments are completed and eligibility is confirmed. Subjects will be considered randomized and in the treatment period once study treatment has been initiated.

Written informed consent/Assignment of subject enrolment/randomization number:

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

- All subjects will be required to provide consent to supply a tumour biopsy sample taken during the screening period for entry into this study. This consent is included in the main subject informed consent form. Please note that subjects are asked to provide separate consent for provision of optional tumour biopsy samples, if willing (see Section 5.6).

- Additionally, subjects will be given the option to consent to the host pharmacogenetics research component and the CSF analysis of the study in separate Informed Consent Forms (ICF).

- As per standard, enrolment number (E-code) is assigned to the subject and Principal Investigator or delegate should perform screening/enrolment call (see Section 3.3). During the randomization visit (Visit 2), subject will receive randomization number and randomized arm information via IVRS/IWRS. For chemotherapy, administration may occur approximately 7 days after randomization due to pre-treatment requirements.

Mandatory screening tumour biopsy sample for mutation analysis:

Tumour sample must be formalin fixed and paraffin embedded (FFPE) and must be biopsied following progression on the latest line of therapy. Samples may be collected from primary or metastatic tumour deposits. Bone samples (including soft tissue tumoral masses emerging from the bone) cannot be accepted for testing. Sites should ship the FFPE tumour sample to the testing laboratory as soon as it is available. Tissue should be less than 60 days old from date of sectioning to date of testing. Blocks must be provided wherever possible. If this is not possible, a minimum of 6 slides of freshly prepared unstained 5-micron sections from this screening tumour block may be provided. See Section 5.6.

The mandatory screening tumour biopsy must not be taken from a previously irradiated lesion (please refer to Inclusion criterion # 10 for details). This biopsy sample is not subject to the 28-day screening window; if tissue is already available from a biopsy taken since documentation of disease progression on the most recent treatment regimen then there is no need for a further biopsy as this sample can be submitted for T790M mutation status. If the first biopsy is not confirmed as T790M mutation positive due to test failure (i.e. an invalid result or invalid run occurred), testing will be repeated and an additional biopsy sample may be requested. If the T790M mutation is not detected in the first biopsy (and the **cobas**® EGFR Mutation Test indicates a valid result), no additional testing for the subject will be performed for this study and an additional biopsy sample WILL NOT be accepted.

Optional second tissue sample for diagnostic development:

The optional second tissue sample (FFPE) may be provided to facilitate diagnostic development and pre-market approval of the diagnostic test. This should be obtained at the same time and as part of the same procedure as the mandatory screening biopsy. Optional tumour biopsy tissue may also be used for companion diagnostic development.

The following will be collected at screening:

Demography:

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

Medical/surgical history:

A standard medical and surgical history will be obtained.

Physical examination including vital signs (pulse and BP), height, weight:

Physical examination includes an assessment of the following: general appearance, respiratory, cardiovascular, skin, head and neck (including ears, eyes, nose and throat), abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

Ophthalmologic assessment:

Measurements of best-corrected visual acuity, intraocular pressure and slit-lamp fundoscopy should be obtained.

Eligibility criteria:

Subjects must not be randomized unless all eligibility criteria have been fully met.

World Health Organization (WHO) Performance Status:

Performance status will be assessed at the visits indicated in the Study Plan (see Table 1, Table 2, Table 3 and Table 4) 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.

Pregnancy test:

Pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) for women of childbearing potential only.

Archival tumour sample (if available):

All subjects will be asked to provide consent to supply a sample of their archival tumour blocks if a sample taken at the time of diagnosis is available. Any archival biopsy samples taken following previous lines of therapy will also be requested, if available. In each case the previous subject treatment must be clearly indicated for each sample provided.
Tumour samples will preferably be in the form of a formalin fixed paraffin embedded block (sample derived from the diagnostic tumour or a metastatic site). If this is not possible, 10-20 slides of freshly prepared unstained 5 micron sections from the archival tumour block may be provided.

Laboratory safety assessments:

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis should be taken. See Section 5.2.1.

If clinical chemistry, haematology and urinalysis assessments have been performed within 14 days pre-randomization they do not have to be repeated prior to commencing treatment on visit 2 Day 1 if the subject's condition has not changed (no new treatment during this period of time, no new complication or aggravation).

Plasma for ctDNA and blood borne biomarkers:

All subjects are required to provide two baseline plasma samples prior to receiving the result of their T790M mutation status result. These baseline samples are not required to be taken again, if the subject is re-screened. All screening plasma samples should be sent to the AstraZeneca (AZ) appointed Clinical Research Organisation (CRO) for retrospective analysis. See Section 5.6.2.

Pharmacogenetics (optional):

Optional genetic blood sample should be taken from consenting subjects at screening. If for any reason the sample is not drawn prior to dosing it may be taken at any visit until the last study visit. See Section 5.5.

Tumour Assessments (RECIST 1.1):

The imaging modalities used for RECIST 1.1 assessments will be CT or MRI scans of chest and abdomen (including liver and adrenal glands). Any other sites where disease is suspected or known at baseline must be also imaged. Baseline assessments should be performed as close as possible to the start of treatment (and prior to randomization). See Section 5.1.1. All imaging assessments including unscheduled visit scans should be collected on an ongoing basis and sent to the AZ appointed CRO to enable central analyses if required.

According to the therapy area standards, base-line assessment should be within 28days of the study treatment start and follow-up assessments will be relative to the date of randomization.

Subjects with known or suspected brain metastases at screening should have a CT/MRI of the brain prior to starting study treatment. These subjects should be followed up on study with repeated CT/MRI assessment, using the same frequency as RECIST assessments. The same modality for CT/MRI should be used for a subject throughout the study. Brain metastases will be assessed as non-target lesions. See Section 5.1.1.

Anti-cancer treatment:

All prior anti-cancer therapy will be collected at screening and end of the study and recorded in the eCRF.

Concomitant medication use:

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the Case Report Form (CRF). See Section 7.7.

Digital ECG:

Three 12-lead ECG should be performed. See Section 5.2.4.

Echocardiogram/ MUGA:

An Echocardiogram or MUGA scan to assess LVEF will be performed at screening (prior to study medication). The modality of the cardiac function assessments must be consistent within a subject ie, if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans. The subjects should also be examined using the same machine and operator whenever possible.

4.2 Treatment period (up to primary PFS analysis)

For subjects receiving AZD9291:

A cycle of treatment is defined as 21 days of once daily AZD9291 treatment. After Cycle 7 Day 1, the duration between study visits will change from every 21 days (3 weeks) to every 42 days (6 weeks).

If a subject continues to receive treatment with AZD9291 beyond RECIST 1.1 defined progression they must continue to follow the treatment visit schedule and assessments excluding study specific RECIST 1.1 assessments.

For subjects randomized to AZD9291, please follow the study schedule described in Table 1.

For subjects receiving platinum-based doublet-chemotherapy:

Folic acid will be administered 5-7 days prior to the 1st dose, then daily during the treatment period until 21 days post the last dose. Vitamin B12 will be administered within 7 days of first infusion and every 9 weeks during the treatment period. Corticosteroid will be adminstered on the day prior to, on the day, and on the day after infusion. Subjects may also receive other pre-treatment/ concomitant treatment as recommended by approved label for pemetrexed, carboplatin or cisplatin as clinically indicated by the investigator.

Platinum-based doublet chemotherapy will be administered every 21 days from previous cycle Day 1. Subjects can continue to receive platinum-based doublet-chemotherapy until matching discontinuation criteria (see Section 3.9) or up to a total of 6 cycles. Each cycle treatment can be interrupted maximum of 21 days. If cycle treatment is delayed by more than 21 days, subject will be permanently discontinued from doublet-chemotherapy. If appropriate, and according to the approved label use or local practice guidelines, pemetrexed may be continued as maintenance treatment.

Subjects who progress according to RECIST 1.1 criteria prior to completion of initial doublet chemotherapy treatment or during pemetrexed maintenance monotherapy may continue with chemotherapy treatment as long as they show clinical benefit, as judged by the investigator.

For subjects receiving platinum-based doublet-chemotherapy, please follow the study schedule in Table 2.

For subjects who cross-over to AZD9291:

Once subjects on the platinum-based doublet chemotherapy arm are determined to have objective radiological progression according to RECIST 1.1 by the investigator and confirmed by independent central imaging review, they will be eligible to receive AZD9291 80mg, once daily and will follow the assessments as per Table 3.

If a subject has been deemed to have objective disease progression according to Investigator tumour assessment by RECIST 1.1, but is not confirmed by independent central imaging review, he/she is not eligible to cross-over to AZD9291 at that time. Should it be in the subject's best interest, and only if further randomized chemotherapy is warranted, he/she may continue to receive randomized doublet chemotherapy (if initial doublet chemotherapy treatment has not yet been completed) or pemetrexed maintenance monotherapy. Sites are to submit the next scheduled tumour assessment for central imaging review according to Table 2.

The following criteria must be met for a subject to cross-over to AZD9291:

- No intervening systemic anti-cancer therapy following discontinuation of randomized chemotherapy treatment.
- At least a 14 day washout period between last dose of randomized chemotherapy and starting cross-over AZD9291 treatment.
- 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.

These subjects may continue treatment with AZD9291 as long as they show clinical benefit, as judged by the investigator.

While RECIST 1.1 assessments are not required to be reported in the RAVE eCRF following confirmation of progression by Independent Central Review, tumour assessments should be done in accordance to local clinical practices.

If subjects are not eligible to cross-over to AZD9291, they will enter into the follow-up phase of the study, and other treatment options should be discussed by the investigator.

The following will be collected during the Treatment Period (described mainly what is not already mentioned under Screening Period, Section 4.1):

Ophthalmologic examination:

To be performed as clinically indicated. 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.

Echocardiogram/MUGA:

To be performed every 12 weeks and as clinically indicated. 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.

Physical examination, including vital signs (pulse and blood pressure), laboratory parameters, ECG:

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.

Plasma for ctDNA and blood borne biomarkers:

All subjects will be requested to provide one plasma sample prior to dosing, at each treatment period study visit.

PK Blood Samples (including metabolites):

For subjects randomized to AZD9291, blood samples (plasma) will be taken to determine concentrations of AZD9291, AZ5104 and AZ7550.

EORTC QLQ-C30, EQ-5D-5L, EORTC QLQ-LC13 and PRO-CTCAE:

Patient reported outcomes will be collected for all subjects throughout the study period via a hand-held electronic device.

Healthcare Resource Use:

Healthcare resource use assessment will be completed by the Investigational Site for any such healthcare resource use between visits.

Concomitant Medication Use:

For subjects randomized to doublet-chemotherapy, Folic acid, Vitamin B12 and Corticosteroid administration will be initiated prior to the start of study treatment.

Descriptions of the procedures for this treatment period are included in Table 1, Table 2 and Table 3.

4.3 Post-Treatment Follow-up period

4.3.1 Discontinuation visit (up to primary PFS analysis)

A Discontinuation Visit will be performed at the time randomized treatment is permanently stopped. A second Discontinuation Visit will be performed for those subjects that stop AZD9291 in the Cross-over Treatment Phase.

For subjects randomized to the platinum-based doublet-chemotherapy, the discontinuation visit should be done after central confirmation of disease progression. The Chemotherapy discontinuation visit and Cross-Over visit can be done on the same day, as long as all other parameters are met.

Refer to Table 1, Table 2 or Table 3 for details.

4.3.2 Twenty-eight Day follow-up (up to primary PFS analysis)

As a minimum, telephone contact should be made with the subject 28(+7) days following the discontinuation of investigational product 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 (up to primary PFS analysis)

Subjects who discontinue study medication for reasons other than objective disease progression will continue RECIST 1.1 assessments every 6 weeks (relative to date of randomization) for objective progression.

If a subject has been deemed to have objective disease progression according to Investigator tumour assessment by RECIST 1.1, but is not confirmed by independent central imaging review, he/she is not eligible to cross-over to AZD9291 at that time. Should it be in the subject's best interest, and only if further randomized chemotherapy is warranted, he/she may continue to receive randomized doublet chemotherapy (if initial doublet chemotherapy treatment has not yet been completed) or pemetrexed maintenance monotherapy. Sites are to submit the next scheduled tumour assessment for central imaging review according to Table 2.

In addition to RECIST 1.1 assessments, the following assessments are also required during this follow-up period as detailed in the Study Plan Table 1, Table 2 or Table 3.

- EORTC QLQ-C30 and EQ-5D-5L every 6 weeks and at the time of progression.
- EORTC QLQ LC13 and PRO-CTCAE every 3 weeks and at the time of progression.
- Plasma for ctDNA collected every 6 weeks up to and including progression (corresponding with the RECIST assessments – and continuing after treatment discontinuation if this is in absence of progression)
- Adverse event collection detailed in Section 6.3
- Anti-cancer therapy and surgery collected every 6 weeks
- WHO performance status should also be collected at other site visits that the subject attends, if appropriate site staff are available to collect such information. In addition, where possible, please provide WHO performance status when information on subsequent anticancer therapy is provided.
- Once subjects on the platinum-based doublet chemotherapy arm are determined to have objective radiological progression according to RECIST 1.1 by the investigator and confirmed by independent central imaging review, they will receive AZD9291 80mg, once daily and will follow the assessments as per Table 3. These subjects may continue treatment with AZD9291 as long as they show clinical benefit, as judged by the investigator.

- Subjects who are not be eligible to cross-over to AZD9291will enter into the follow-up phase of the study, and other treatment options should be discussed by the investigator.

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

Assessments for survival should be made every 6 weeks following objective disease progression. Survival information may be obtained via telephone contact with the subject, the subject's family or caretaker or by contact with the subject'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, Table 2, Table 3 or Table 4):

- EORTC QLQ-C30 and EQ-5D-5L every 6 weeks.
- EORTC QLQ LC13 and PRO-CTCAE every 3 weeks.
- 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 (to inform PFS2 endpoint). PFS2 is only required for primary PFS analysis and the first OS analysis. Post the first OS analysis DCO, the information is not required to be collected.
- WHO performance status should also be collected at other site visits that the subject attends, if appropriate site staff are available to collect such information. In addition, where possible, please provide WHO performance status when information on subsequent anticancer therapy is provided.

Survival data will be collected up to the time of the final OS analysis. Subjects should be contacted in the week following the data cut-off for the final survival analyses to provide complete survival data.

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

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

The primary PFS analysis will occur when at least 221 progression events have been observed out of the 410 globally randomized subjects.

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

Following the primary PFS analysis subjects still on the platinum-based doublet chemotherapy arm will be given the opportunity to begin treatment with AZD9291 80mg, once daily if it is considered in the patients best interest by the Investigator and they are eligible to receive

AZD9291 (no contraindications). These subjects may continue treatment with AZD9291 as long as they show clinical benefit, as judged by the investigator. If subjects are not given AZD9291 at the discretion of the investigator, they will enter into the follow-up phase of the study, and other treatment options should be discussed by the investigator.

Patients on study treatment will be followed for survival, PRO and core safety assessments (haematology, clinical chemistry, AEs/SAEs and concomitant medications (including any subsequent cancer therapy), study treatment dosing details as per Table 4.

Post the first OS DCO, the duration between study visits will change to every 84 days (12 weeks).

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

4.3.6 Patient management post final (OS) analysis

The final (third) analysis of overall survival will be performed when the OS data are approximately 70% mature (approximately 287 death events). At this time point, the clinical study database will close to new data. Patients are, however, permitted to continue to receive study treatment (AZD9291) beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from treatment. Dispensing of study treatment post final OS analysis DCO will be done outside of IWRS. Patients who remain on study treatment after this time point will be monitored according to routine clinical practice as defined by the Investigator. At routine clinic visits, patients will return used and unused medication, and a thorough drug accountability assessment will be performed at the site.

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

5. STUDY ASSESSMENTS

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

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

For details of data and study management see Section 9.4 of Clinical Study Protocol.

5.1 Efficacy assessments

5.1.1 RECIST 1.1

All imaging assessments including unscheduled visit scans should be collected on an ongoing basis and sent to an AstraZeneca (AZ) appointed Clinical Research Organisation (CRO) to enable independent central analyses.

For both investigator and Blinded Independent Central Review (BICR) RECIST 1.1 criteria will be used to assess each subject's tumour response to treatment and allow calculation of PFS, ORR, DCR, DoR and assess tumour shrinkage. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria [CR (complete response), PR (partial response), SD (stable disease) or PD (progression of disease)] are presented in Appendix G. For ORR, a visit response of CR or PR must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed. See Section 4 for considerations related to RECIST 1.1 assessments.

The methods used at baseline for assessment of tumour burden [CT or MRI scans of chest and abdomen (including liver and adrenal glands)] must be used at each subsequent follow-up assessment. Any other areas of disease involvement should be additionally investigated based on the signs and symptoms of individual subjects. The baseline assessment should be performed within 28 days of the start of randomized treatment. Up to the primary PFS analysis, subsequent assessments are to be performed every 6 weeks relative to randomization until objective disease progression. 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 subject has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Any other sites at which new disease is suspected should also be appropriately imaged. For subjects under consideration for cross-over to AZD9291, scheduled tumour assessments will continue until confirmation of objective radiological disease progression by independent central imaging review according to RECIST 1.1, if even after investigator has deemed objective disease progression.

Following the primary PFS analysis, subjects still on the platinum-based doublet chemotherapy arm will be given the opportunity to begin treatment with AZD9291 80 mg, once daily if it is considered by the Investigator to be in the patient's best interest, and if they are eligible to receive AZD9291 (no contraindications). At least a 14 day washout period is required between last dose of chemotherapy and starting AZD9291 treatment.

For subjects not or no longer under consideration, or ineligible to cross-over to AZD9291 (e.g. subjects randomized to the chemotherapy arm, but not meeting criteria to cross-over to

AZD9291; subjects originally randomized to the AZD9291 arm; or subjects who already crossed-over to AZD9291), no subsequent tumour assessments are expected to be sent for independent central imaging analysis after the investigator confirms objective disease progression.

Post the primary PFS analysis, tumour assessment will be performed in accordance with clinical practice and scans will no longer be centrally collected apart from subjects included in the China cohort. For China cohort, tumours assessment will be continued up to PFS analysis for China cohort until at least 20 PFS events have been observed out of approximately 50 Chinese subjects. After the China PFS analysis, tumour assessment will be performed in accordance with clinical practice and scans will no longer be centrally collected.

Subjects with known or suspected brain metastases at screening should have a CT/MRI of the brain prior to starting study treatment. These subjects should be followed up on study with repeated CT/MRI assessment, using the same frequency as RECIST assessments. The same modality for CT/MRI should be used for a subject throughout the study. Brain metastases will be assessed as non-target lesions.

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 subject's status. If repeat 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 non-target disease, there must be an overall substantial worsening in non-target disease 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 non-target lesions 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 1.1 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 (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

The primary PFS analysis for this study will be based on the tumour assessments using investigator site assessments according to RECIST 1.1.

5.1.2 RECIST 1.1 – Blinded Independent Central Review (BICR) Assessment

All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed CRO to enable central analysis. The central review will provide confirmation of progression for patients on platinum-based doublet chemotherapy who have progressed, as assessed by the investigator, at the request of the investigational site for confirmation of progression prior to starting AZD9291. Otherwise, the results of this

independent central review will not be communicated to the investigational site, and the management of subjects will be based on the result of RECIST 1.1 assessments conducted by the investigator. Up to the primary PFS analysis, since confirmation by central imaging review is required for subjects to cross-over to AZD9291, no subjects will be permitted to cross-over without the aforementioned confirmation. A sensitivity analysis will be conducted to identify any potential biases in the investigator assessments compared with BICR according to RECIST 1.1 (see Section 8.5.1).

After the primary PFS analysis, any imaging for tumour assessments will not be required to be submitted for BICR, apart from subjects included in the China cohort. For China cohort, imaging assessment will be continued up to PFS analysis for China cohort until at least 20 PFS events have been observed out of approximately 50 Chinese subjects. After the China PFS analysis, any imaging for tumour assessments will not be required to be submitted for BICR for China cohort.

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 (Table 1, Table 2, Table 3 or Table 4).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection 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. 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 5 Laboratory Safety Variables

Clinical chemistry	Haematology
Serum (S)/Plasma (P)-Albumin	Blood (B)-Haemoglobin
S/P-ALT	B-Leukocyte
S/P-AST	B-Haematocrit
S/P-Alkaline phosphatase	B-Red blood cell (RBC) count
S/P-Bilirubin, total	B-Absolute leukocyte differential count:
S/P-Calcium, total	Neutrophils
S/P-Creatinine	Lymphocytes

Table 5 Laboratory Safety Variables

Clinical chemistry	Haematology
S/P-Glucose (fasting, on PK days only) [1]	Monocytes
S/P-Lactate dehydrogenase (LDH) [2]	
S/P-HbA1C	Basophils
S/P-Magnesium	Eosinophils
S/P-Potassium	B-Platelet count
S/P-Sodium	B-Reticulocytes
S/P-Urea nitrogen/Blood urea nitrogen (BUN)	Urinalysis
	U-Glucose
	U-Protein
	U-Blood

[1] Patients in AZD9291 cohort 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. Fasting is not required for patients in chemo cohort.
[2] 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 females 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 centre as source data for laboratory variables. For information on how Adverse Events (AEs) based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a subject shows an AST **or** ALT ≥3xULN **and** 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).

5.2.2 Volume of blood

Total mandatory blood volume for AZD9291 subjects in first 9 weeks is 172 mL (Table 6).

Table 6 Blood sample volumes AZD9291 subjects

Visit	Safety (mL)[1]	PK Analysis (mL)	Plasma (mL)	PGx (mL)
Screening	15		20	10 (optional)
Cycle 1	45	6	30	
Cycle 2	15	NA	10	
Cycle 3	15	6	10	
SUBTOTAL (mandatory)	**90**	**12**	**70**	

[1]For safety, assumes 6 mL clinical chemistry and 9 mL haematology per visit

Total mandatory blood volume for Platinum-based Doublet-chemotherapy subjects in first 9 weeks is 160 mL (Table 7).

Table 7 Blood sample volumes Platinum-based Doublet-chemotherapy subjects

Visit	Safety (mL)[1]	PK Analysis (mL)	Plasma (mL)	PGx (mL)
Screening	15		20	10 (optional)
Cycle 1	45	NA	30	
Cycle 2	15	NA	10	
Cycle 3 (onwards)	15	NA	10	
TOTAL (mandatory)	**90**		**70**	

[1] For safety, assumes 6 mL clinical chemistry and 9 mL haematology per visit

5.2.3 Physical examination

All subjects will have a physical examination performed at the time points indicated in the Study Plan (Table 1, Table 2, Table 3 or Table 4), 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, musculo-skeletal (including spine and extremities), and neurological systems.

5.2.4 ECG

All subjects will have three 12-lead ECG performed at the time points indicated in Study Plan (Table 1, Table 2, Table 3 or Table 4). A twelve-lead ECG will be obtained after the subject has been resting semi-supine for at least 10 minutes prior to times indicated and should be recorded at 25 mm/sec. All ECGs should be recorded with the subject in the same physical position. For each time point three ECG recordings should be taken at approximately 5 minute intervals. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study if possible. Prior to first OS analysis DCO,

digital ECG recordings will be collected, analysed and stored by a central ECG vendor. Post first OS analysis DCO, ECGs will be collected locally and stored at the site.

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 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.

Heart rate, PR, R-R, QRS and QT 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.

Patients who experience a QTcF interval greater than 500 msec on at least 2 separate ECGs must have AZD9291 treatment interrupted until the QTcF interval is less than 481 msec or recovery to baseline if baseline QTcF is greater than or equal to 481 msec, then restart at a reduced dose (40 mg).

Patients experiencing QTcF interval prolongation with signs/symptoms of serious arrhythmia will not be permitted to restart study treatment.

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

5.2.5 Echocardiogram/MUGA scan

An Echocardiogram or MUGA scan to assess LVEF will be performed at screening (prior to study medication) and every 12 weeks (± 1 week window interval) relative to randomization. The modality of the cardiac function assessments must be consistent within a patient ie, if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans. The subjects should also be examined using the same machine and operator whenever possible. A 28-day follow-up assessment will be required if an on treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm

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

5.2.6 Vital signs

5.2.6.1 Pulse, blood pressure, weight and height

Supine blood pressure and pulse rate will be measured after 10 minutes rest. Assessments will be performed at the visits as shown in the Study Plan (see Table 1, Table 2, Table 3 or Table 4). Additionally at the discretion of the investigator if clinically indicated.

Weight will be performed at screening and then Day 1 of each cycle and at the discontinuation visit. Weight will be documented in kilogram (e.g. 68.5 kg) in eCRF.

Height will be assessed at screening only and will be documented in centimeters (e.g. 168 cm) in eCRF.

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

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 obtained. For any subject who experiences visual symptoms (including blurring of vision), additional tests may be conducted throughout the study period, if clinically indicated (see Table 1, Table 2 or Table 4).
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.

Subjects experiencing corneal ulceration will not be permitted to restart study treatment.

Ophthalmologic exams to be performed as clinically indicated. 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.

Ophthalmology examination results should be collected in the eCRF.

5.3 Other assessments

5.3.1 Baseline characteristics

Baseline demographics, disease history, previous treatments and EGFR mutation information will be collected.

5.3.2 Patient reported outcomes

Patient reported outcomes (PROs), an umbrella term referring to all outcomes and symptoms, are directly reported by the subject. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered: EORTC QLQ C-30, QLQ-LC13, EQ-5D-5L and PRO CTCAE (see Appendix F). PROs will be collected until end of study (including survival follow-up period) and at the time of progression unless consent is withdrawn or patient is lost to follow up as indicated in the Study Plan (Table 1, Table 2, Table 3 or Table 4).

5.3.2.1 EORTC QLQ-C30 and 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 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 F. The QLQ LC13 includes questions assessing cough, haemoptysis, dyspnoea and site specific pain (symptoms), sore mouth, dysphagia, peripheral neuropathy and alopecia (treatment-related side effects) and pain medication.

5.3.2.2 EQ-5D-5L

The EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.

The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty (EuroQol Group 2013).

Since 2009, the EuroQol group has been developing a more sensitive version of the EQ-5D (the EQ-5D-5L), which expands the range of responses to each dimension from 3 to 5 levels of increasing severity (Herdman et al 2011). Preliminary studies indicate that the 5L version improves upon the properties of the 3L measure in terms of reduced ceiling effect, increased reliability and an improved ability to differentiate between different levels of health (Pickard et al 2007, Janssen et al 2008, Janssen et al 2008b).

The subject will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual

analogue scale, where the subject will be asked to rate current health status on a scale of zero to 100, with zero being the worst imaginable health state (see Appendix F).

5.3.2.3 PRO-CTCAE

The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (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, German and Spanish. PRO-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 et al 1992; Litwin et al 1988-1992; Basch et al 2009). To date, 81 symptoms of the CTCAE (version 4) 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 F).

5.3.2.4 Administration of electronic PROs

Subjects 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 subjects 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 subject has any medical problems he/she should discuss them with the doctor or research nurse separately from the ePRO assessment
- Remind subjects that there are no right or wrong answers, avoid bias by not clarifying items
- Train the subject 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.

In order to minimize missing data, compliance must be checked frequently to identify problems early. If compliance drops below 85%, a check-in call from the site to ask the subject if he/she has any difficulties is highly recommended. Up to primary PFS analysis, the

assessment will be performed as shown in the Study Plan (see Table 1, Table 2 and Table 3). After primary PFS analysis and up to the final OS analysis DCO, the assessment will be performed as shown in Table 4. After final OS analysis, all PRO data will no longer be collected.

5.3.2.5 Healthcare resource use

The site will ask subjects for any healthcare resource use between visits (ie, excluding routine follow up clinic visits associated with the clinical trial but including both planned and unplanned admissions) during the treatment period and at the 28-day follow-up.

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
- Treatment related to Adverse Events (including the method of delivery of the treatment)
- Treatment not related to the study.

The above resource use data will mainly come from the subject's medical record and will be captured by site staff using WBDC. After primary PFS analysis, healthcare resource use information will continue to be collected until the first OS analysis DCO. After the first OS analysis DCO, the information will not be collected.

5.4 Pharmacokinetics

5.4.1 Collection of samples for subjects randomized to AZD9291

Three venous blood samples per visit in time windows Pre-dose, 0.5 to 1.5, and 2 to 4 hours for determination of total concentrations of AZD9291 and metabolites (AZ5104 and AZ7550) in plasma will be taken at the times presented in Table 8.

The date and time of collection of each sample and the date and time of dose (on PK sampling day and for previous dose) will be recorded.

Table 8 PK blood sample schedule (Pre-dose, 0.5 to 1.5, and 2 to 4 hours)

Time relative to dose	**Cycle 1 -Visit 2**	**Cycle 3 -Visit 6**	**Cycle 5 -Visit 8**	**Cycle 7 -Visit 10** and every other cycle up to and including Cycle 13
mL	**6 (2 mL x 3)**	**6 (2 mL x 3)**	**6 (2 mL x 3)**	**6 (2 mL x 3)**

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

No PK blood samples will be collected in subjects crossed-over from chemotherapy treatment.

5.4.2 Determination of drug concentration

Samples for determination of AZD9291 (and metabolite) concentrations in plasma and cerebrospinal fluid (CSF) will be collected and analysed by Covance on behalf of AstraZeneca, using an appropriate bioanalytical method. 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 (ie, AZD9291, AZ5104 and AZ7550) at the time of receipt by the bioanalytical laboratory will be analysed.

In addition, the pharmacokinetic samples may be subjected to further analyses by AstraZeneca in order to further investigate the presence and/or identity of additional drug metabolites. Any results from such analyses will be reported separately from the Clinical Study Report.

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 after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic 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 Clinical Study Report 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 the AZ Biobank or it's designee; see details in the Laboratory Manual).

5.4.4 Collection of cerebrospinal fluid – optional

For subjects randomized to AZD9291: If the subject agrees, and upon signature of optional ICF, a sample of CSF will be obtained at one time point taken at any time from Cycle 2 Day 1 onwards. Samples will be collected, labelled and stored and shipped as detailed in the laboratory manual.

Any residual CSF after PK analysis may be used for exploratory research into factors that may influence development of NSCLC and/or response to AZD9291. If possible, the CSF sample should be taken on the same day as planned PK samples.

5.5 Pharmacogenetics

If a subject 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 my contribute to the risk of NSCLC (for example, but not limited to, mutations in the gene encoding EGFR)

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

5.5.1 Collection of pharmacogenetic samples

The subject'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 subjects immediately 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 subjects who may withdraw due to an adverse event. Such subjects 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 subject for genetics during the study.

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

5.5.2 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 subject confidentiality. Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the Clinical Study Report 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 C for details of the optional (DNA) genetic research.

5.6 Exploratory Research

If a subject agrees to participate in the exploratory biomarker research component of the study biological samples (e.g., plasma, serum, archived and study-obtained tumour, etc.) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of investigational product and clinical outcomes.

The results of this exploratory biomarker research will be reported separately and will not form part of the Clinical Study Report.

The results of this exploratory biomarker research may be pooled with biomarker data from other studies with the investigational product to generate hypotheses to be tested in future studies.

5.6.1 Collection of Tumour Biopsy Samples

5.6.1.1 Archival Tumour

All subjects eligible for the study will be asked to provide consent to supply a sample of their archival tumour blocks if a sample taken at the time of diagnosis is available (blocks preferred, slides acceptable).

Only submit samples for subjects who have a centrally confirmed T790M+ mutation. Any archival biopsy samples taken following previous lines of therapy will also be requested, if available. In each case the previous patient treatment must be clearly indicated for each sample provided. This sample will be used to support exploratory biomarker analyses (see Section 5.6).

5.6.1.2 Optional Tissue Collection at Screening

Subjects will be asked to consent to provide additional tumour tissue at screening, which can be collected at the same time as the mandatory screening tumour biopsy (see Section 4.1), where appropriate to do so. This biopsy will be used to support the development of the diagnostic test for pre-market approval by FDA (US) and/or for exploratory biomarker analyses (see Section 5.6).

5.6.1.3 Discontinuation Biopsy

Subjects will also be asked to consent to a further optional biopsy, to be collected at discontinuation of study treatment. This sample will be used to support exploratory biomarker analyses (see Section 5.6).

For timings of tumour biopsies see Table 9.

Table 9 Tumour biopsy samples

Time relative to dose	Requirement
Archival	M*
Screening	M + O[2]
Discontinuation or progression[1]	O

[1] *To be taken at discontinuation or progression, whichever occurs first*
[2] *Only block tissue sample will accepted*
M = Mandatory O = Optional M* = mandatory if available

Tumour samples should be provided in the form of a formalin fixed paraffin embedded block (tissue derived from the diagnostic tumour or a metastatic site). If this is not possible, the following may be provided:

- 12-20 slides of freshly prepared unstained 5-micron sections from the mandatory screening FFPE tumour block may be provided

- 10-20 slides of freshly prepared unstained 5-micron sections from the archival tumour block may be provided.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

5.6.2 Collection of exploratory samples – blood-borne biomarkers and ctDNA

Up to primary PFS analysis, all subjects 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 may be used to further investigate the relationship between PK and blood-borne biomarkers. The ctDNA samples will be used to further explore EGFR (and other gene) mutation status and may be used to develop a plasma-based diagnostic test.

Plasma samples will be taken at the following times (pre-dose):

- Screening
- Cycle 1 - Day 1, Day 8 & 15; Cycle 2, 3, 4, 5, 6 – Day 1; thereafter
- Every 6 weeks up to and including progression (corresponding with the RECIST assessments)
- Discontinuation of study drug (if subject continues after progression on AZD9291)

The samples will be analysed for a range of oncology biomarkers, which may correlate with drug response. Post primary PFS analysis, ctDNA samples will continue to be collected at treatment discontinuation and at progression.

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

5.7 Management of Biological Samples

5.7.1 Storage, re-use and destruction of biological samples

Biological samples for future research will be retained at AstraZeneca or it's designee for a maximum of 15 years following the finalisation of the Clinical Study Report, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the investigational product to generate hypotheses to be tested in future research.

5.7.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B '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 subject 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 to the AstraZeneca designated central Contract Research Organisation.

5.7.3 Chain of custody of biological samples

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

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

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

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

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

5.7.4 Withdrawal of Informed Consent for donated biological samples

If a subject 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.

As collection of the biological samples is an optional part of the study, then the subject may continue in the study.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the 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 subject 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 and the action documented and 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.

5.8 Post progression outcomes

The date of second progression (PFS2) will be recorded by the Investigator and defined according to local standard clinical practice and may involve any of the following: objective radiological evidence (preferred), symptomatic progression or death. Second progression status will be reviewed every 6 weeks following the progression event used for the primary variable PFS (the first progression) and status recorded.

PFS2 is only required for primary PFS analysis and the first OS analysis. Post the first OS analysis DCO, the information is not required to be collected.

The start and stop date, and details of the type of all subsequent anticancer treatments will be recorded.

PRO data and WHO performance status will be collected post progression (see Section 4).

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product,

whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). 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 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. Any deterioration of the disease targeted in the study and associated symptoms should not be regarded as an adverse event.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, 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 subject or may require medical intervention to prevent one of the outcomes listed above.

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the treatment period and including the safety follow-up period. The follow-up period is defined as 28 days after study treatment is discontinued. SAEs occurring in the follow-up period should be reported to AstraZeneca in the usual manner (see Section 6.4).

Following discontinuation of study treatment, SAEs considered related to study procedures should continue to be collected while subjects are followed up for disease progression as outlined in Table 10.

After the final OS database lock, there may be some subjects remaining on study treatment. For these subjects who are continuing to receive AZD9291 AstraZeneca will collect information (during the treatment period and for 28 (+ 7) days after last dose) on SAEs,

overdose and pregnancy via paper and emailed (preferably) or faxed directly to TCS (also known as AZ DES). Drug accountability information will be recorded in the patient notes.

For each subject who discontinues study treatment for a reason other than disease progression:

- Follow-up information on all ongoing AEs should continue to be collected to the survival follow-up
- SAEs considered related to study procedures must continue to be collected and reported to AstraZeneca using standard SAE timelines and process until the end of progression follow up (ie, disease progression)
- All deaths must continue to be collected after progression and during the survival follow-up

Table 10 Summary of recording and follow-up of adverse events and deaths

	From ICF to Treatment Period (Screening Period)	Until 28-day Follow-up Visit (safety follow-up period)	Post 28-day Follow-up visit but prior to progression (if applicable)	Post 28-day Follow-up visit and post progression (survival follow-up period)
Collect all new AEs in CRF	Yes	Yes	No	No
Collect all ongoing AEs in CRF	Yes	Yes	Yes	Yes
Collect all study procedure-related SAEs in CRF	Yes	Yes*	Yes*	Yes*
Death due to AE, or unknown cause[1]	Yes	Yes*	No	No

1 for example, death not due to disease progression or related to study procedure - refer to Section 6.3.10

* Post final OS analysis DCO, recording and follow up of SAEs will be done via paper

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE:

- AE (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 Investigational Product (yes or no)
- Action taken with regard to investigational product
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE 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 AE.

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 Investigational Product and each Adverse Event, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

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

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

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject 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 CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording 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 clinical study report. 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 investigational product 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 subject shows an AST or ALT ≥3xULN and 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 subject meets potential Hy's law (PHL) criteria.

Details of identification of PHL 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 subject's condition attributable to the disease for which the investigational product 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.

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 treatment and have been identified after the subject'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 investigational product, 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 CRF 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.

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 are needed for a decision on whether or not expedited reporting is required.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day ie, 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, 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 WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC 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 is the IB for the AstraZeneca drug AZD9291 and the EU Summary of Product Characteristics (SPC) for the active comparator product (including any AstraZeneca comparator).

6.5 Overdose

There is no definition of what constitutes an overdose. In the Phase I study, 355 patients with advanced NSCLC were administered AZD9291 at single and multiple oral doses ranging from 20 mg to 240 mg daily (as of data cut-off date 02 December 2014). All doses were well tolerated. Experiences of excessive doses (i.e. in excess of the optimal 80 mg indicated dose) in this study did not show any DLTs or acute toxicities.

There is no known antidote. Investigators will be advised that any patient who receives a higher dose than that 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 CRF and on the Overdose CRF module
- An overdose without associated symptoms is only reported on the Overdose CRF module

If an overdose occurs in the course of the study, then the Investigator or other site personnel inform 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 course of the study and within 6 weeks of the last dose of AZD9291 (for female subjects) or within 4 months of the last dose for female partners of male subjects (see section 6.6.2 for more details)

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study, study treatment 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 subject was discontinued from the study.

If any pregnancy occurs in the course of the study or within 6 weeks of the final dose of the investigational product then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day ie, 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 subject's partners is not considered to be an adverse event. 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 subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome; the male subject 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 dose until six months after dosing should be followed up and documented.

6.7 Management of toxicities related to AZD9291

If a subject experiences a CTCAE grade 3 and/or unacceptable toxicity not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

Patients with QTcF prolongation to >500 msec should have study treatment interrupted and regular ECGs performed until resolution to <481 msec or recovery to baseline (if baseline QTcF is >481 msec), and then restarted at a reduced dose of 40mg. If the QTcF does not resolve to < 481 msec or baseline within 21 days the patient will be permanently withdrawn from study treatment.

If the toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset, treatment with AZD9291 may be restarted at the same dose (80 mg) or a lower dose (40 mg) using the rules below for dose modifications (Table 11) and with discussion and agreement with the AstraZeneca Study Team Physician as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption.

If the toxicity does not resolve to ≤CTCAE grade 2 after 3 weeks, then the subject should be withdrawn from the study and observed until resolution of the toxicity.

Table 11 Dose Interventions

Intervention	AZD9291 Dose
Starting Dose	80 mg
Reduced Dose	40 mg

On resolution of toxicity within 3 weeks:

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

If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca study team must be informed. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters) will be captured in the RAVE eCRF. All image data should also be provided to AstraZeneca. 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 interstitial lung disease should be considered and study treatment must be permanently discontinued.

In the absence of a diagnosis of interstitial lung disease study treatment may be restarted following consultation with the AstraZeneca Study Team Physician.

Subjects experiencing any of the following will not be permitted to restart study treatment:

- Corneal ulceration
- Interstitial Lung Disease (ILD)
- QTc interval prolongation with signs/symptoms of serious arrhythmia

6.7.1 Skin reactions

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

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

Changes in the characteristics of skin reactions will be collected in the "SKNREAC" CRF.

Changes in the CTCAE grade of skin reactions will be collected in the AE CRF.

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 as per investigator discretion, as per the standard local medical practice. Skin biopsies should ideally be taken in subjects with clinically significant or grade ≥ 3 skin reaction.

6.7.2 Diarrhoea

Recommendations for appropriate management of diarrhoea, including dose-adjustments for adverse events of diarrhoea that are of CTCAE grade ≥3 or that are clinically significant and/or intolerable and considered by the investigator to be causally related to AZD9291, will be provided to investigators. Changes in CTCAE grade of diarrhoea will be captured in the AE eCRF.

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

6.8 Management of toxicities related to Platinum-Based Doublet Chemotherapy

Detailed here, as guidance, are the US (FDA) approved toxicity management guidelines for pemetrexed, carboplatin and cisplatin (US Prescribing Information).

For toxicity management please adhere to these guidelines or, where appropriate, to local approved or clinical practice guidelines. A discussion with AZ study physician would be indicated in case of using local clinical practice guidelines.

6.8.1 Dose Adjustment Recommendations for Carboplatin

Pretreatment platelet count and performance status are important prognostic factors for severity of myelosuppression in previously treated patients.

The suggested dose adjustments for single agent or combination therapy shown in the table below are modified from controlled trials in previously treated and untreated patients with ovarian carcinoma. Blood counts were done weekly, and the recommendations are based on the lowest post-treatment platelet or neutrophil value.

Platelets	Neutrophils	Adjusted Dose* (From Prior Course)
>100 000	>2 000	125%
50-100 000	500-2 000	No Adjustment
<50 000	<500	75%

* Percentages apply to carboplatin for Injection, USP as a single-agent or to both carboplatin and cyclophosphamide in combination. In the controlled studies, dosages were also adjusted at a lower level (50% to 60%) for severe myelosuppression. Escalations above 125% were not recommended for these studies.

Carboplatin is usually administered by an infusion lasting 15 minutes or longer. No pre- or post-treatment hydration or forced diuresis is required.

Patients with Impaired Kidney Function:

Baseline Creatinine Clearance	Recommended Dose on Day 1
41 mL/min - 59 mL/min	250 mg/m^2
16 mL/min - 40 mL/min	200 mg/m^2

Patients with creatinine clearance values below 60 mL/min are at increased risk of severe bone marrow suppression. In renally impaired patients who received single-agent carboplatin therapy, the incidence of severe leukopenia, neutropenia, or thrombocytopenia has been about 25% when the dosage modifications in the table below have been used.

The data available for patients with severely impaired kidney function (creatinine clearance below 15 mL/min) are too limited to permit a recommendation for treatment.

These dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance based on the degree of bone marrow suppression.

6.8.2 Precaution for Cisplatin

Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurologic examination should also be performed regularly.

6.8.3 Dose Adjustment Recommendations for Pemetrexed and Cisplatin

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy. Treatment

may be delayed to allow sufficient time for recovery. Upon recovery, patients should be retreated using the guidelines in below Tables, which are suitable for using pemetrexed as a single-agent or in combination with cisplatin. Please follow this recommendation for pemetrexed when dosed together with carboplatin

Dose Reduction for Pemetrexed (single-agent or in combination) and Cisplatin - Hematologic Toxicities:

Nadir ANC <500/mm^3 and nadir platelets ≥50000/mm^3	75% of previous dose (pemetrexed and cisplatin).
Nadir platelets <50 000/mm^3 without bleeding regardless of nadir ANC	75% of previous dose (pemetrexed and cisplatin).
Nadir platelets <50 000/mm^3 with bleeding, regardless of nadir ANC	50% of previous dose (pemetrexed and cisplatin).

If patients develop non-hematologic toxicities (excluding neurotoxicity) ≥Grade 3, treatment should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to guidelines in below Table.

Dose Reduction for Pemetrexed (single-agent or in combination) and Cisplatin – Non-hematologic Toxicities[a,b]

	Dose of Pemetrexed (mg/m^2)	**Dose of Cisplatin (mg/m^2)**
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

[a] NCI Common Toxicity Criteria (CTC)
[b] excluding neurotoxicity (see Table below).

In the event of neurotoxicity, the recommended dose adjustments for pemetrexed and cisplatin are described in below Table. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

Dose Reduction for Pemetrexed (single-agent or in combination) and Cisplatin – Neurotoxicity:

CTC Grade	**Dose of Pemetrexed (mg/m^2)**	**Dose of Cisplatin (mg/m^2)**
0-1	100% of previous dose	100% of previous dose

2	100% of previous dose	50% of previous dose

Discontinuation Recommendation: Pemetrexed therapy should be discontinued if patient experiences any hematologic or nonhematologic Grade 3 or 4 toxicity after two dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

Renally Impaired Patients: In clinical studies, patients with creatinine clearance ≥45 mL/min required no dose adjustments other than those recommended for all patients. Insufficient numbers of patients with creatinine clearance below 45 mL/min have been treated to make dosage recommendations for this group of patients. Therefore, pemetrexed should not be administered to patients whose creatinine clearance is <45 mL/min using the standard Cockcroft and Gault formula (below) or GFR measured by Tc99m-DTPA serum clearance method:

Males:	$\frac{[140 - \text{Age in years}] \times \text{Actual Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}} = \text{mL/min}$
Females:	Estimated creatinine clearance for males × 0.85

Caution should be exercised when administering Pemetrexed concurrently with NSAIDs to patients whose creatinine clearance is <80 mL/min.

6.9 Study governance and oversight

6.9.1 Steering Committee

A Steering Committee comprising of the principal investigators for study D5160C00003, in addition to principal investigators from the other AZD9291 pivotal studies will provide advice on any aspect of the study design or conduct based on requests from the sponsor and assure consistency across the entire AZD9291 pivotal programme.

No Data Monitoring Committee (DMC) is planned, as the safety profile of AZD9291 from the ongoing phase I trial in a similar NSCLC patient population is modest, predictable with no reported life-threatening adverse events. There is therefore no requirement for pre-planned specified expert independent safety reviews in this study.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity and Dose of investigational product – AZD9291

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

AstraZeneca will supply AZD9291 as tablets for oral administration as a single daily dose of 80 mg. Tablets can be taken whole with approximately 240 mL water, with or without regard to food. Subjects will be required to fast (water only) for at least 8 hours prior to the collection of a fasting glucose sample as per the study plan (Table 1) and Section 5.2.1.

At each dispensing visit, sufficient AZD9291 for 21, 42, or 84 days treatment, (depending on study schedule) plus overage, will be distributed. Prior to the final DCO, individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS. Dispensing of study treatment post final OS DCO will be completed outside of the IVRS/IWRS system.

Subjects should swallow one AZD9291 80 mg tablets once daily, commencing on Cycle 1 Day 1. Tablets should be taken whole with water, with or without food.

The initial dose of 80 mg AZD9291 can be reduced to 40 mg AZD9291 once daily under circumstances described in Section 6.7

On clinic days on which PK samples are scheduled, the dosing should be delayed until arrival at the clinic. Subjects 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 subject 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 dose time, the missed dose should not be taken, and subjects should be instructed to take the next dose at the next scheduled time. If a subject vomits after taking their AZD9291, they should not make up for this dose, but should take the next scheduled dose.

Prior to the final OS DCO, any change from dosing schedule, dose interruptions, dose reductions should be recorded in the eCRF. Post final OS DCO, drug accountability information will be stored in the patient notes at the site.

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

Additional information about the Investigational product may be found in the Investigators' Brochure.

7.2 Identity and Dose of Comparator Product – Platinum-based Doublet-Chemotherapy

Comparator product	Dosing
pemetrexed + carboplatin	500mg/m^2 AUC5 on Day 1 of every 21d cycle
pemetrexed + cisplatin	500mg/m^2 75mg/m^2 on Day 1 of every 21d cycle

Platinum-based Doublet-chemotherapy is available in a range of strengths and will be sourced locally or centrally and should be administered according to local prescribing information, including any treatment restrictions.

To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4mg of dexamethasone administered orally twice a day.

To reduce toxicity, subjects treated with pemetrexed must also receive vitamin supplementation. Subjects must take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the approximately 7 days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Subjects must also receive vitamin B12 (e.g. i.m.1000 micrograms or equivalent) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 doses may be given on the same day as pemetrexed. Subjects may also receive other pre-treatment / concomitant treatment as recommended by approved label for pemetrexed, carboplatin or cisplatin as clinically indicated by the investigator.

Anticipated treatment duration is approximately six months.

7.3 Labelling

Labels for IP (if required also for chemotherapy) will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text will be translated into local language.

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

7.4 Storage

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

7.5 Compliance

Prior to the final OS DCO the administration of all study treatments (including investigational products) should be recorded in the appropriate sections of the Case Report Form. Post final OS DCO, drug accountability information will be stored in the patient notes at the site.

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

7.6 Accountability

The investigational product provided for this study will be used only as directed in the study protocol.

The study personnel will account for all investigational products dispensed to and returned from the subject.

The study personnel at the investigational site will account for all treatments dispensed and for appropriate destruction. Certificates of delivery and destruction should be signed.

7.7 Concomitant and other treatments

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the CRF. After permanent discontinuation of study treatment and 28 day follow up, only subsequent regimens of anti-cancer therapy will be recored in CRF. If medically feasible, subjects taking regular medication, with the exception of potent inducers of CYP3A4 (see Appendix D), should be maintained on it throughout the study period. Subjects taking concomitant medications whose disposition is dependent upon BCRP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving AZD9291. Guidance on medications that require close monitoring is given in Appendix E.

Patients taking rosuvastatin (due to BCRP mediated increase in exposure) should have CPK levels monitored. If the subject experiences any potentially relevant adverse events suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosurvastatin should be stopped, and any appropriate further management should be taken.

Subjects taking warfarin should be monitored regularly for changes in prothrombin time or INR.

Other anticancer agents, investigational agents and radiotherapy should not be given while the subject is on study treatment.

Pre-medication will be allowed for subjects randomized to the doublet chemotherapy arm. It is also allowed for subjects randomized to AZD9291, but not before the first dose of AZD9291. This includes management of diarrhoea, nausea and vomiting.

Leukocycte-depleted blood transfusions are allowed at any time during the study.

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

Subjects may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases. Subjects may also receive radiotherapy or medication (e.g. denosumab) for painful bony metastases. For questions related to specific mediations, please contact the Study Physician.

Supportive care and other medications that are considered necessary for the subject's well-being, may be given at the discretion of the investigator.

Study Treatment (Subjects randomized to AZD9291)

Tablets should be taken whole with approximately 240 mL water, with or without regard to food.

Study Treatment (Subjects randomized to platinum-based doublet chemotherapy)

Platinum-based doublet chemotherapy should be administered according to local prescribing information, including any treatment restrictions.

Prohibited Medication/Class of drug:	**Usage:**
Other anticancer agents, investigational agents and radiotherapy	Should not be given while the subject is on study treatment.

Rescue/Supportive Medication/Class of drug:	**Usage:**

Pre-medication will be allowed for subjects randomized to the doublet chemotherapy arm. It is also allowed for subjects randomized to AZD9291, but not before the first dose of AZD9291.	To be administered as directed by the investigator. This includes management of diarrhoea, nausea and vomiting.
Blood transfusions	Allowed at any time during the study.
Granulocyte colony stimulating factors	Should not be used prophylactically during Cycle 1. Use of prophylactic colony stimulating factors may be considered after Cycle 1 following discussion with the AstraZeneca Study Team Physician.
Corticosteroids and/or bisphosphonates	Subjects may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases.
Palliative radiation	Subjects may receive radiotherapy for painful bony metastases.
Supportive care and other medications that are considered necessary for the subject's well-being	To be administered as directed by the investigator (e.g. denosumab for painful bony metastases).

7.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form. Some medications may be limited due to their QT potential, please refer to Appendix E.

7.8 Post Study Access to Study Treatment

Subjects receiving AZD9291 at the time of study completion (ie, after final OS DCO date) may continue to receive AZD9291, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment. Study treatment will continue until a study discontinuation criterion (eg, withdrawal of consent, adverse event, clinical progression, or no longer deriving benefit) has been met as assessed by the investigator. Investigators will report all SAEs, overdose and pregnancy to the sponsor until 28 days after receipt of their last dose of study treatment. Post final OS analysis DCO, recording and follow up of SAEs will be done via paper. Drug accountability data will also be collected. Assessments will revert to standard of care at their particular site.

A CSR addendum will be prepared to summarise any additional safety data collected.

7.9 Cross-over to AZD9291

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

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalised prior to first subject in (FSI). The aim of the study is to compare the efficacy and safety of AZD9291 versus platinum-based doublet chemotherapy. All analyses will be performed by AstraZeneca or its representatives.

The primary analysis will be performed when at least 221 PFS events have occurred, so that the PFS data are approximately 54% mature. Three analyses of OS are planned; two interim analyses and final analysis. The data cut-off for the first analysis of overall survival will be conducted approximately 4 months after data cut-off for the primary analysis of PFS and the second analysis will be conducted when the OS data are approximately 50% mature (approximately 205 death events). A final analysis of overall survival will be performed when the OS data are approximately 70% mature (approximately 287 death events).

Multiple Testing Strategy

In order to describe the benefits of AZD9291 treatment, the primary and secondary endpoints will be tested at a 2-sided significance level of 5%.

However, in order to provide strong control of the type I error rate (2-sided 5%), the primary endpoint of PFS and key efficacy secondary endpoints, ORR and OS will be tested in this sequential order. If any previous analysis in the sequence is not statistically significant, the alpha spending cannot be transferred to subsequent analyses. A 2-sided 5% alpha will be used in all testing, with the exception of overall survival endpoint. Since three analyses of OS are planned, the Lan DeMets approach that approximates the O'Brien and Fleming spending function will be used to maintain an overall 2-sided 5% type I error across the three planned analyses of OS. Note, any non-statistically significant analyses at the interims will not preclude further testing of OS.

For PRO symptoms and health related quality of life endpoints, the overall type I error (5% 2 sided) will be controlled across the five primary PRO measures of cough, dyspnoea and pain as assessed by the EORTC QLQ-LC13 and fatigue and appetite loss as assessed by the EORTC QLQ-C30 using the Bonferroni-Holm procedure.

The physical functioning and global health status/QoL domains of the EORTC QLQ-C30 are pre-specified endpoints of interest.

8.2 Sample size estimate

PFS is the primary endpoint for this study. Approximately 410 subjects will be randomized in a 2:1 ratio (AZD9291: chemotherapy) to this study.

The primary analysis of PFS will occur when at least 221 progression events have been observed out of the 410 globally randomized subjects. With 221 progression events, the study

will have at least 80% power to show a statistically significant PFS at the 5% 2-sided significance level if the assumed treatment effect were HR 0.67; this translates to a 3 month improvement on an estimated median PFS of 6 months on the control arm, assuming PFS is exponentially distributed. The smallest treatment difference that would be statistically significant is a PFS HR of 0.76 (this translates into an approximate 2 month improvement on an estimated median PFS of 6 months on the control arm, assuming PFS is exponentially distributed).Assuming 15 months non-linear recruitment, 221 PFS events are expected to occur approximately 20 months after the first subject is randomized in the study.

In order to randomize 410 subjects assuming a 10% screen failure rate, 455 T790M+ subjects will need to be enrolled. In order to enrol 455 T790M+ subjects, 1034 subjects will need to be screened [assuming 827 (55%) of subjects are T790+ and allowing for a 20% attrition rate].

8.3 Definitions of analysis sets

8.3.1 Full analysis set

The full analysis set will include all randomized subjects prior to the end of global recruitment. Any subjects randomized 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 randomized treatment, regardless of the treatment actually received.

8.3.2 Safety analysis set

The safety analysis set will consist of all subjects randomized prior to the end of global recruitment who received at least one dose of randomized treatment and for whom post dose data are available. Any subjects randomized 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 subjects (e.g., those randomized to treatment A but actually given treatment B) will be summarised according to the treatment they actually received.

8.3.3 PK analysis set

Subjects in the Full Analysis Set 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 needs to be present for that sample.

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 imagining scans, the RECIST tumour response data will be used to determine each subject's visit response according to RECIST version 1.1. It will also be used to determine the endpoints ORR, DoR, DCR and PFS from the overall visit response and scan dates.

At each visit, subjects will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessments. If a subject has had a tumour assessment, which cannot be evaluated, then the subject will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Appendix G for the definitions of Complete Response, Partial Response, Stable Disease and Progressive Disease.

Blinded Independent Central Review of RECIST based assessments

The Blinded Independent Central Review of radiological imagining data will be carried out using RECIST version 1.1. All radiological scans for all subjects (including those at unscheduled visits, or outside visit windows) will be provided to the BICR. The imaging scans will be reviewed by two independent radiologists using RECIST 1.1 criteria and will be adjudicated if required. The independent reviewers will be blinded to treatment. For each subject, the BICR will define the overall visit response data (CR, PR, SD, PD or NE) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). If a subject has had a tumour assessment, which cannot be evaluated, then the subject will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD

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

Progression Free Survival (PFS)

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

However, if the subject progresses or dies after two or more missed visits, the subject will be censored at the time of the latest evaluable RECIST assessment. If the subject has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two 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 subject for PFS the subject will be censored at the latest of the dates contributing to a particular overall visit assessment

Objective Response Rate (ORR)

ORR rate is defined as the number (%) of subjects with measurable disease with at least one visit response of CR or PR that is confirmed at least 4 weeks later. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any complete response or partial response, which occurred after a further anticancer therapy was received, will not be included in the numerator for the ORR calculation.

In the case where a subject has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the subject will be defined as a responder. Similarly, if a subject has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

Duration of Response (DoR)

Duration of response will be defined as the time from the date of first documented response, (that is subsequently confirmed) until 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 subject does not progress following a response, then their duration of response will use the PFS censoring time.

Disease control rate (DCR)

Disease control rate is defined as the percentage of subjects who have a best overall response of CR or PR or SD.

Tumour shrinkage

Tumour shrinkage will be assessed using RECIST tumour response. The absolute change and percentage change from baseline in 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 anticancer therapy.

Overall Survival (OS)

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

Note: Survival calls will be made in the 2 weeks following the date of the data cut-off for each OS analysis, and if subjects are confirmed to be alive, or if the death date is post the final data

cut-off date, these subjects will be censored at the date of the final data cut off. Death dates may be found by checking publicly available death registries.

HRQoL & Symptoms

Patient reported outcomes will be assessed using the EORTC QLQ-C30 and QLQ-LC13 questionnaires. The 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 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/symptom items, the functional scales and the global health status scale in the QLQ-C30 and for each of the symptom scales/items in the 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 three questions: “Were you short of breath when you rested; walked; climbed stairs”),
- cough: one item (“How much did you cough?”),
- pain: one item (“Have you had pain in your chest”).
- fatigue (a composite score of three items: “Did you need rest; Have you felt weak; Were you tired”)
- appetite loss: one individual item (“Have you lacked appetite”)

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 ≥10 for scales/items from the QLQ-LC13 and the QLQ-C30 (Osoba et al 1998).

For example, a clinically meaningful deterioration or worsening in chest pain (as assessed by QLQ-LC13) is defined as an increase in the score from baseline of ≥10. A clinically meaningful improvement in fatigue (as assessed by 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 12.

Table 12 Visit Response for HRQoL and disease-related symptoms

Score	Change from baseline	Visit Response
LC13 symptom scales/items	≥+10	Worsened
	≤-10	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

Time to symptom deterioration

For each of the symptoms scales/items in QLQ-LC13, time to symptom deterioration will be defined as the time from randomization until the date of first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the subject withdraws from randomized therapy or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within two visits of the last PRO assessment where the symptom change could be evaluated.

Subjects whose symptoms (as measured by QLQ-LC13) 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 two or more missed PRO assessment visits or the subject dies after two or more missed PRO assessment visits, the subject will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a subject 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 ITT population who have baseline scores ≤ 90.

Symptom Improvement Rate

The symptom improvement rate will be defined as the number (%) of subjects with two consecutive assessments at least 18 days apart (ie, 21 days allowing a visit window of 3 days), which showed a clinically meaningful improvement (a decrease from baseline score ≥10 for

LC13 scales/items or C30 scales/items) in that symptom from baseline. The denominator will consist of a subset of the ITT population who have a baseline symptom score ≥10.

Mixed Models Repeated Measures (MMRM) Analysis

Change from baseline in cough, dyspnoea and pain scores as assessed by the EORTC QLQ-LC13 and fatigue and appetite loss as assessed by the EORTC QLQ-C30 will be the primary analysis and assessment of PRO outcome measures. The analysis will be performed using a linear mixed model for repeated measures (MMRM) analysis of change from baseline in the scores for each visit.

Symptom improvement rate and Time to symptom deterioration analyses will be considered as supportive analyses.

Time from randomization to second progression (PFS2) (exploratory)

Time from randomization to second progression (PFS2) is defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the primary variable PFS or death. Subjects 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, ie, censored at the last progression assessment date if the subject has not had a second progression or death.

Time to first subsequent therapy or death (TFST)

Time to first subsequent therapy or death is defined as the time from the date of randomization to the earlier of the date of anticancer therapy start date following study treatment discontinuation, or death. Any subject 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, ie, the last follow-up visit where this was confirmed.

Time to second subsequent therapy or death (TSST)

Time to second subsequent therapy or death is defined as the time from the date of randomization to the earlier of the date of second subsequent anticancer therapy start date following study treatment discontinuation, or death. Any subject not known to have died at the time of the analysis and not known to have had a second further intervention of this type will be censored at the last known time to have not received second subsequent therapy, ie, the last follow-up visit where this was confirmed.

Patient reporting of CTCAE symptoms

The PRO-CTCAE questionnaire will be used to derive subject reporting of CTCAE symptoms.

Health State Utility

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses). Where values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied. In addition to the descriptive system, respondents also assess their health on the day of assessment on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

Health Resource Utilisation

Health resource utilisation will be assessed in terms of hospitalization, outpatient visits and emergency department visits

8.4.2 Calculation or derivation of safety variable(s)

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs (pulse and BP) and ECG. These will be collected for all subjects.

Adverse events

AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by subject.

Any AE occurring before treatment with AZD9291 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 investigational product (ie, the last dose of AZD9291/chemotherapy) will be included in the AE summaries. Any events in this period that occur after a subject has received further therapy for cancer (following discontinuation of AZD9291) will be flagged in the data listings. Please refer to Section 6.3.1

Other significant adverse events (OAEs)

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 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 could be 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 AZ5104 and AZ7550 will be performed by Quantitative Clinical Pharmacology, AZ or delegate on behalf of Quantitative Clinical Pharmacology. Plasma concentration will be summarized by normal time window. The ratio of metabolite to AZD9291 will be calculated.

The plasma concentration data for AZD9291 and metabolites will also be analysed using a population pharmacokinetic approach, which may include exploring the influence of covariates on PK, if the data allows. A pharmacokinetic-pharmacodynamic approach will be used to investigate the relationship between PK and selected primary, secondary and/or exploratory endpoints, where deemed appropriate. Results may be reported separately from the Clinical Study Report for the main study.

The data collected in this study may also be combined with similar data from other studies and explored using population pharmacokinetic and/or pharmacokinetic-pharmacodynamic method. The results of any such analyses will be reported separately from the Clinical Study Report.

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 and 2-sided p-value.

8.5.1 Analysis of the primary variable (s)

PFS will be analyzed using a log rank test stratified by ethnicity (Asian, Non-Asian) for generation of the p-value and using the Breslow approach for handling ties. The hazard ratio (HR) and confidence interval will be obtained directly from the U and V statistics as follows (Berry G et al 1991, Selke & Siegmund 1982):

$$HR = \exp(U/V)$$

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

Where $U = \Sigma_i(d_{1i} - e_{1i})$ is the log-rank test statistic (with d_{1i} and e_{1i} the observed and expected events in group 1) and $\sqrt{V}$ the standard deviation of the log-rank test statistic obtained from the LIFETEST procedure with a STRATA term for the stratification variable.

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

Subgroup analysis

Subgroup analyses will be conducted by comparing PFS between treatments in the following groups:

- Ethnicity (Asian versus Non-Asian)
- Gender (Male versus Female)
- Age at randomisation (<65 versus ≥65)
- Mutation status prior to start of study (ex19 versus L858R)
- Duration of prior EGFR TKI (<6 months, ≥6 months)
- Brain metastases at entry
- Smoking history

The HR (AZD9291: chemotherapy) and associated CI will be calculated from a Cox proportional hazards model (ties=Efron) that contains the treatment term, factor and treatment-by-factor interaction term. The treatment effect HRs for each treatment comparison along with their confidence intervals will be obtained for each level of the subgroup from this single model. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI from the overall population (using the primary analysis).

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.

No adjustment to the significance level for testing will be made since the subgroup analysis will be considered exploratory and may only be supportive of the primary analysis of PFS.

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 1985.

Sensitivity analyses

(a) Ascertainment bias

The possibility of bias in assessment and measurement of PFS by investigators will be assessed by comparing the hazard ratios derived from investigator review with the hazard ratio derived using the blinded independent central review assessment of disease progression by RECIST.

(b) 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 analyzed using a stratified log rank test, as described for the primary analysis of PFS. For patients who die in the absence of progression, the date of death will be used to derive the PFS time used in the analysis.

(c) 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 subjects who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumour assessments will be included. In addition, subjects 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.

(d) Exploratory Analysis

Recently, it has been suggested that, in order to assess the potential for bias amongst investigators, a BICR amongst only a sample of subjects could be performed; if evidence of bias is detected, according to a pre-defined threshold, the BICR is then assessed in all subjects, otherwise it is concluded the sample was sufficient to rule-out meaningful levels of bias. A proposed sample BICR method has been submitted to a peer reviewed statistical journal for publication as of August 2014 and in order to demonstrate that this is a valid methodology for use in future trials, an exploratory analysis will be carried out using this methodology. Further details will be provided in the SAP.

8.5.2 Analysis of the secondary variable(s)

8.5.2.1 Analysis of ORR

ORR will be analyzed using a logistic regression with a covariate for ethnicity (Asian, Non-Asian). 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. The p-value will be based on twice the change in log-likelihood resulting from the addition of a treatment factor to a model that contains the covariates defined above.

8.5.2.2 Analysis of DoR

In order to analyze the secondary outcome variable of Duration of Response between arms the Expected Duration of Response (EDoR) will be derived for each treatment arm (Ellis S et al 2008). The EDoR is the product of the proportion of subjects responding to treatment and the mean DoR in responding subjects, and provides an estimate based on all randomized subjects. Treatments will be compared by calculating the ratio of EDoRs using an appropriate probability distribution for duration of response in responding subjects. 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 duration of response in responding subjects, including associated Kaplan-Meier curves (without any formal comparison of or p-value attached).

8.5.2.3 Analysis of DCR

DCR will be analyzed using a logistic regression with a covariate for ethnicity (Asian, Non-Asian). 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. The p-value will be based on twice the change in log-likelihood resulting from the addition of a treatment factor to a model that contains the covariates defined above.

8.5.2.4 Analysis of Tumour Shrinkage

The best absolute change in target lesion tumour size from baseline and percentage change in target lesion tumour size from baseline will be summarized using descriptive statistics and presented at each timepoint and by randomized treatment group. The effect of AZD9291 on percentage change in tumour size will be estimated from an analysis of covariance (ANCOVA) model with a covariate for ethnicity (Asian, Non-Asian). The number of subjects, unadjusted mean and lsmeans for each treatment group will be presented, together with the difference in lsmeans, 95% confidence interval and corresponding p-value.

8.5.2.5 Analysis of OS

OS data will be analyzed 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). Two interim analyses of OS will be performed and a final, optional analysis of OS may be performed. The first interim analysis of OS will be performed at the time of the primary analysis of PFS. The second interim analysis of OS will be performed when the OS data are approximately 50% mature.

8.5.2.6 Analysis of Time to PRO Symptom Deterioration

Time to PRO symptom deterioration will be analyzed using a log rank test stratified by ethnicity (Asian, Non-Asian) for generation of the p-value and using the Breslow approach for handling ties. The hazard ratio (HR) and confidence interval will be estimated using the same methods as for the primary endpoint of PFS, as described in Section 8.5.1.

8.5.2.7 Analysis of PRO Symptom Improvement Rate

Symptom Improvement Rate will be analyzed using a logistic regression with a covariate for ethnicity (Asian, Non-Asian). 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. The p-value will be based on twice the change in log-likelihood resulting from the addition of a treatment factor to a model that contains the covariates defined above.

8.5.2.8 Pharmacokinetics

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

8.5.2.9 Patients with EGFR T790M mutation status detected in baseline plasma sample (ctDNA)

The efficacy of AZD9291 versus chemotherapy will be evaluated for the subgroups of patients with T790M detected in their baseline plasma sample and patients that are T790M negative by the plasma test. For PFS, the HR and associated 95% CI will be calculated and KM plots presented for each group. For ORR, the odds ratio and associated 95% CI will be presented for each group.

8.5.3 Exploratory analysis

PRO-CTCAE

PRO-CTCAE data will be presented using summaries and descriptive statistics based on the Full Analysis Set and further details will be provided in the SAP.

Healthcare Resource Use

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

Exploratory analysis of post progression outcomes

PFS2 will be analysed using the same method as the analysis of PFS. Time to first subsequent therapy, time to second subsequent therapy and time to change in symptoms (measured by PRO HRQoL questionnaires) will be summarised as appropriate and further details will be provided in the SAP.

Exploratory analysis of characterising survival

All further analysis of overall survival will be exploratory. The effect of baseline characteristics on overall survival in each randomized 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).

Additional analysis of overall survival adjusting for the impact of subjects randomized to chemotherapy, who subsequently receive a 3rd generation EGFR TKI with T790M activity (ie, those who "switch" treatment) may be completed if this treatment sequence occurs in a significant proportion of subjects. Methods such as Rank Preserving Structural Failure Time (RPSFT) (Robins et al 1991), Inverse Probability of Censoring Weighting (IPCW) (Robins et al 1993) and other methods in development may be explored. The decision to adjust and final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions.

Further detail will be provided in the SAP and Payer Analysis Plan.

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

In order to adequately compare the efficacy and safety of AZD9291 versus chemotherapy in Chinese patients to fulfil China FDA requirements, subjects recruited in China after global recruitment has ended will be combined with any subjects recruited from China prior to the end of the global recruitment. This China-only cohort will be analysed and reported separately from the Clinical Study Report.

8.6.1 Definition of China analysis sets

8.6.1.1 China-only Full Analysis Set

The China-only Full analysis set will include all subjects randomized in China. This includes all subjects randomized in China prior to the end of global recruitment and all additional subjects recruited in mainland China after global recruitment is completed.

The China-only Full analysis set will be used for all China-only efficacy analyses and treatment groups will be compared on the basis of randomized study treatment, regardless of the treatment actually received.

8.6.1.2 China-only Safety Analysis Set

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

8.6.1.3 China-only Pharmacokinetic Analysis Set

The China-only Pharmacokinetic Analysis Set is defined as subjects in the China-only FAS who have at least one evaluable PK concentration.

8.6.2 China-only analyses

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 will be repeated for the China-only cohort using the analysis sets described in Section 8.6.1.

All statistical analyses will be considered exploratory and only performed if sufficient numbers of events or subjects 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 not be stratified by ethnicity (Asian versus Non-Asian).

The analyses be performed at the time of the primary PFS analysis if at least 20 PFS events have been observed out of approximately 50 Chinese subjects, otherwise summaries of efficacy will be provided only. Additional follow-up of Chinese subjects if deemed appropriate may be performed when the PFS data are more mature (for example, 70% maturity, as consistent with the primary global PFS analysis).

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

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

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

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

9.2 Monitoring of the study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in

accordance with the Laboratory Manual and that investigational product accountability checks are being performed

- This study plans to follow the principles of targeted monitoring and perform 100% Source Data Verification (SDV) on critical variables (including eligibility criteria) only. The expected overall SDV will be at least 50%
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

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

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

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

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

9.2.3 Archiving of study documents

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

9.3 Study timetable and end of study

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

The study is expected to start in Q3 2014 and to end by approximately Q4 2018.

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

9.4 Data management by AstraZeneca

Data management will be performed by Cognizant Data Management Centre staff, according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the Cognizant Data Management Centre.

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 (SAE) 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.

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 vendor to Cognizant Data Management Centre.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Subject data protection

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

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

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

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

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

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

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form are to be 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, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

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

10.4 Informed consent

The Principal Investigator(s) at each centre will:

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

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the 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 Ethics Committee 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 Ethics Committee see Section 10.3.

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

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

10.6 Audits and inspections

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

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B

- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations

- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging

- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Pharmacogenetics Research

BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the AZD9291 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD9291. Collection of deoxyribonucleic acid (DNA) samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD9291 but also susceptibility to the 'response'/disease for which AZD9291 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to AZD9291.

GENETIC RESEARCH PLAN AND PROCEDURES

Selection of genetic research population

Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol, Section 3.1.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main body of the Clinical Study Protocol, Section 3.2.

Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.7 and 3.8 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 1 or after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 1, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 5.2.2 of the Clinical Study Protocol.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the main Clinical Study Protocol.

Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

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

STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

LIST OF REFERENCES

None

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

1. INTRODUCTION

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

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

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

2. DEFINITIONS

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

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

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

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

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

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

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available.
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

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

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

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

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

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
- The 'Medically Important' serious criterion should be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

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

This section is applicable to subjects who meet PHL criteria on study treatment (including the 28 day follow-up period post discontinuation of study treatment) having previously met PHL criteria at a study visit prior to starting study treatment.

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

- Determine if there has been a significant change in the subjects' condition compared with the last visit where PHL criteria were met
- If there is no significant change no action is required
- If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section 4.2 of this Appendix.

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

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

This section is applicable when a patient meets PHL criteria on study treatment (including the 28-day follow-up period) and has already met PHL criteria at a previous on study treatment visit.

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

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

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

If No: Follow the process described in Section 4.2 of this Appendix

If Yes: Determine if there has been a significant change in the patient's condition compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

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

8. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix E Guidance regarding Potential Interactions With Concomitant Medications

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

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

AZD9291 is metabolised by CYP3A4 and CYP3A5 enzymes.

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

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

Table 1 Drugs inducing CYP3A4

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

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

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

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

Table 2 Exposure, pharmacological action and toxicity may be increased by AZD9291

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

3. DRUGS THAT MAY PROLONG QT INTERVAL

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm.

3.1. Drugs known to prolong QT interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with AZD9291. Recommended withdrawal periods following cessation of treatment with these agents are provided in the table.

Table 3 Drugs prolonging QT interval

Contraindicated drug	Withdrawal period prior to AZD9291 start
Clarithromycin, droperidol, erythromycin, procainamide	**2 days**
Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	**7 days**
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	**14 days**
Levomethadyl, methadone, pimozide	**4 weeks**
Arsenic trioxide	**6 weeks***
Pentamidine	**8 weeks**
Amiodarone, chloroquine	**1 year**

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

3.2. Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Table 4 Drugs that may prolong QT interval

Drug	Minimum treatment period on medication prior to AZD9291 start
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isridipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	**2 days**
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprin-sulfa, trimipramine, voriconazole	**7 days**
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	**14 days**
Fluoxetine	**5 weeks**
Protriptyline	**6 weeks**
Tamoxifen	**8 weeks**

Appendix F Patient Reported Outcomes (EOR-QLQ-C30, EOR-QLQ-LC13, PRO-CTCAE and EQ-5D-5L)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

English Version of selected PRO-CTCAE items:

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days…

RASH	
Did you have any RASH?	
O Yes	O No

DRY SKIN				
What was the SEVERITY of your DRY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

ACNE OR PIMPLES ON THE FACE OR CHEST				
What was the SEVERITY of your ACNE OR PIMPLES ON THE FACE OR CHEST at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

HAIR LOSS				
Did you have any HAIR LOSS?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

HAND-FOOT SYNDROME(A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS, OR PAIN)				
What was the SEVERITY of your HAND-FOOT SYNDROME (A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS OR PAIN) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

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ITCHY SKIN				
What was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

FINGERNAILS OR TOENAILS	
Did you lose any FINGERNAILS OR TOENAILS?	
O Yes	O No

RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS	
Did you have any RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS?	
O Yes	O No

CHANGE IN COLOR OF YOUR FINGERNAILS OR TOENAILS	
Did you have any CHANGE IN COLOR OF YOUR FINGERNAILS OR TOENAILS?	
O Yes	O No

ARM OR LEG SWELLING			
How OFTEN did you have ARM OR LEG SWELLING?			
O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your ARM OR LEG SWELLING at its WORST?			
O Mild	O Moderate	O Severe	O Very severe
How much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities?			
O A little bit	O Somewhat	O Quite a bit	O Very much

PROBLEMS WITH TASTING FOOD OR DRINK				
What was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

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DECREASED APPETITE				
What was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

NAUSEA				
How OFTEN do you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

VOMITING				
How OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

CONSTIPATION				
What was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

LOOSE OR WATERY STOOLS (DIARRHEA)				
How OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

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PAIN IN THE ABDOMEN (BELLY)				
How OFTEN did you have PAIN IN THE ABDOMEN (BELLY)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did PAIN IN THE ABDOMEN (BELLY) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

LOSE CONTROL OF BOWEL MOVEMENTS				
How OFTEN did you LOSE CONTROL OF BOWEL MOVEMENTS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
How much did LOSS OF CONTROL OF BOWEL MOVEMENTS INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

FATIGUE, TIREDNESS OR LACK OF ENERGY				
What was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

NUMBNESS OR TINGLING IN YOUR HANDS OR FEET				
What was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

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BLURRY VISION				
What was the SEVERITY of your BLURRY VISION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did BLURRY VISION INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

DRY MOUTH				
What was the SEVERITY of your DRY MOUTH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

MOUTH AND THROAT SORES				
What was the SEVERITY of your MOUTH AND THROAT SORES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did MOUTH AND THROAT SORES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

SKIN CRACKING AT THE CORNERS OF YOUR MOUTH				
What was the SEVERITY of SKIN CRACKING AT THE CORNERS OF YOUR MOUTH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

INCREASED SKIN SENSITIVITY TO SUNLIGHT	
Did you have any INCREASED SKIN SENSIVITY TO SUNLIGHT?	
O Yes	O No

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NOSEBLEEDS				
How OFTEN did you have NOSEBLEEDS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your NOSEBLEEDS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

BRUISE EASILY (BLACK AND BLUE MARKS)	
Did you BRUISE EASILY?	
O Yes	O No

SHIVERING OR SHAKING CHILLS				
How OFTEN did you have SHIVERING OR SHAKING CHILLS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

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Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

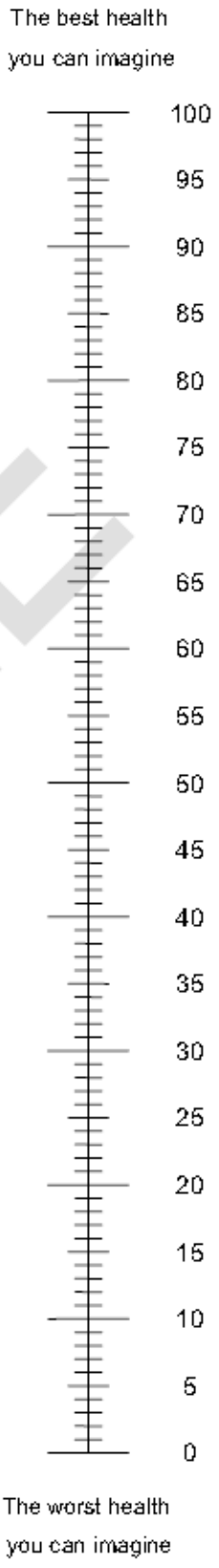
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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

1. INTRODUCTION

This appendix details the implementation of RECIST (Response Evaluation Criteria in Solid Tumours) 1.1 guidelines (Eisenhauer et al 2009) for the study with regards to investigator assessment of tumour burden including protocol-specific requirements for this study.

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

Subjects with at least one lesion measurable that can be accurately assessed at baseline by computerised tomography (CT), magnetic resonance imaging (MRI) or plain X-ray should be included in this study.

Measurable lesions

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

Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline. Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs)
- Truly non-measurable lesions include the following:
- Bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by CT or MRI
- Previously irradiated lesions as localised post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTLs at baseline and followed up as part of the NTL assessment

- Lesions chosen for biopsy during the study screening period if still present should be selected as NTL at baseline and follow up as part of the NTL assessment unless they fulfil the critieria for measurability when there is only one measurable lesion
- Skin lesions assessed by clinical examination
- Brain metastasis

Special cases

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient; these non-cystic lesions should be selected as the target lesions (TLs).

Target lesions

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

Non-target lesions

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

3. METHODS OF MEASUREMENT

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

The methods to be used for RECIST assessment are summarised in **Table 13** and those excluded for tumour assessments in this study are discussed below, with the rationale provided.

Table 13 Summary of Methods of Assessment

Target Lesions	Non target lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, chest X-ray	X-ray, chest X-ray
		Ultrasound
		Bone scan
		FDG-PET

3.1 CT and MRI

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

In this study it is recommended that CT examinations of the chest and abdomen will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For assessment of brain lesions MRI is the preferred method.

3.2 Clinical examination

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are then assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in subjects that also have other lesions assessable by CT, MRI or plain X-ray and to identify the presence of new lesions.

3.3 X-rays

3.3.1 Plain X-ray

Plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

3.3.2 Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

3.4 Ultrasound

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

3.5 Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

3.6 Tumour markers

Tumour markers will not be used for tumour response assessments per RECIST 1.1.

3.7 Cytology and histology

Histology will not be used as part of the tumour response assessment per RECIST 1.1.

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

3.8 Isotopic bone scan

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

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

3.9 FDG-PET scan

FDG-PET (fluorodeoxyglucose positron emission tomography) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

CT examinations of the chest and abdomen (including liver adrenal glands) will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contract media administration is the preferred method. MRI should be used where CT is no feasible or it is medically contra-indicated.

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual subjects and should be performed no more than 28 days before the start of study treatment. CT/MRI scan of the brain should be performed in subjects with known or suspected brain metastases. Follow-up assessments should be performed every 6 weeks (± 7 days) after randomization until discontinuation of study treatment or withdrawal of consent. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

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

4.2 Target lesions

4.2.1 Documentation of target lesions

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

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

Special cases:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s)
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion
- When a TL has had any intervention e.g. radiotherapy, embolization, surgery etc., during the study, the size of the TL should still be provided where possible

4.2.2 Evaluation of target lesions

Table 14 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 14 Overall Visit Response for Target Lesions

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

4.3 Non-Target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator. Table 15 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 15 Overall Visit Response for Non-Target Lesions

Complete Response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more NTLs.

Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST clinically significant for the physician to consider changing or stopping therapy.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit. Note: For subjects without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

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

4.4 New Lesions

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

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

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

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

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

Subjects with 'symptomatic deterioration' requiring discontinuation of study treatment without objective evidence of disease progression at that time should continue to undergo RECIST 1.1 assessments according to the clinical study protocol until objective disease progression is observed.

4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 16.

Table 16 Overall Visit Response

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
IR = incomplete response, NE = not evaluable, NA = not applicable (relevant when no NTLs at baseline)

5. CONFIRMATION OF RESPONSE

In this study, imaging for confirmation of response (CR or PR) should be performed at the next scheduled RECIST assessment

6. CENTRAL REVIEW

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

7. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 45 (2009) 228-247.