Clinical Study Protocol

Drug Substance	AZD3759
Study Code	D6030C00001
Version	6.0
Date	

A Phase I, Open-label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumour Activity of AZD3759 or AZD9291 in Patients with EGFR Mutation Positive Advanced Stage Non Small Cell Lung Cancer (NSCLC)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

For contact details of AstraZeneca personnel see Section 8.1.

VERSION HISTORY

Version 6.0,

Changes to the protocol are summarised below,

The key revision in CSP version 6.0 was to include a final data cut-off date (DCO) for patients dosed with AZD9291. The final DCO is defined as 15 months after last patient starts dosing with AZD9291 or 50% OS maturity of AZD9291 T790M+ LM sub-cohort (whichever occurs latest.) The final DCO may happen earlier than 15 months if both median OS and median duration of response can be assessed earlier. The data analysis will be reported as an addendum to the clinical study report. In addition, LANO (Neuro-Oncology (RANO) adapted for assessment of LM) criteria were added for the central reading of scans.

- Section 1.3 Exploratory objective has been updated to include the best LM Blind Independent Central Review (BICR) assessment for AZD9291 LM patients.
- Section 5.4 has been updated to be consistent with Section 5.5.
- Section 5.5 has been updated to clarify that the study is ongoing until the last visit of the last patient undergoing the study
- Section 6.3.4 ECG section was amended to clarify that after the primary DCO, ECGs for AZD9291 LM patients will be performed via local ECG until final DCO.
- Section 6.4.3 has been updated to be consistent with Section 5.5.
- Section 6.6 Exploratory research section has been updated with the LANO assessment score change. and to be consistent with section 5.5
- Section 6.8.1.1 Central reading of scans has been updated to include the LANO criteria.
- Section 7.4 PK section has been updated to include flexible language around the PK parameters.
- Section 7.5, omitted the derivation of the Overall Survival endpoint and moved this description into Section 7.6 because this variable is regarded as secondary rather than exploratory, as described in section 7.1 (definition of study endpoints). LANO assessment has been added.
- Section 7.6 has been updated to keep consistency with statistical analysis.
- Section 7.8 has been updated to keep consistency with statistical analysis.

- Section 8.1 contact information has been updated.
- Appendix E: Visit Response (extracranial and CNS disease) was updated to keep consistency with eCRF instruction.
- Appendix G: The correct version was inserted.

Version 5.0,

Changes to the protocol are summarised below.

The main purpose of this amendment is to add a sub-cohort of T790M+ LM patients into the AZD9291 LM cohort.

- In Section 2.1.2, add that AZD9291 has been approved in the US to treat patients with metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy
- In Section 2.2.1, update the clinical efficacy data of AZD3759 observed in Part A of this study
- In Section 3.1, remove the sentence regarding the patient randomization to AZD3759 and AZD9291 treatment cohort based on the patient recruitment strategy which prioritizes AZD9291 cohort over AZD3759 cohort
- In Sections 3.1 and 3.2, add that a sub-cohort of T790M+ LM patients will be enrolled within AZD9291 LM expansion cohort
- In Section 4.1, add the inclusion criteria #15 for AZD9291 sub-cohort of T790M+ LM patients and indicate that new patients in AZD9291 cohort will be enrolled via this criteria
- In Section 4.2, clarify that the criteria "Patients currently receiving steroids will not be excluded from the study" does not apply for patients in AZD3759 BM expansion, to keep consistency with inclusion criteria #9 in Section 4.1
- In Section 5.3, add the benefit-risk assessment for patients in AZD3759 BM expansion cohort based on the data from Part A
- In Section 6.1 and 6.3.1, add that for patients in AZD9291 T790M+ LM sub-cohort, a sample will be taken during screening for central confirmation of T790M+ mutation status

- In Section 7.2, revise the target value for BM cohort based on more extensive review of published reports of EGFR TKI therapy
- In Section 7.8, correct the reference line in waterfall plot.
- Remove three references which are not cited in the CSP and correct a few typos throughout the CSP
- Changes made across the CSP due to the template revamp (refer to below table for the comparison of old and new CSP template)

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Version 4.0 [redacted]
Changes to the protocol are summarised below.
In Part A of the study, AZD3759 has achieved C trough free plasma and CSF exposure above pEGFR IC50 of EGFR M+ cells at the doses≥100mg bid. In a heavily pre-treated patients population 8 patients showed tumor shrinkage in the brain among 18 evaluable patients, with 1 confirmed PR and 3 unconfirmed PR at doses≥50mg bid per RECSIT. These evidences support AZD3759 to be investigated in EGFR TKI-naive setting in patients with brain metastasis disease. Therefore, the key revision Amendment 3 was to revise the patient criteria in Part B-BM expansion to "patients who have not received any EGFR TKI and have asymptomatic brain metastasis, either found during screening process which does not require local treatment in the opinion of the investigator or local treatment has been given (surgery or radiation), patient is stable without corticosteroid and/or anti-convulsants treatment for at least 2 weeks before study enrolment." based on above emerging data. The details are summarised as follows: • Add contact details of Principal Investigators at the beginning of the protocol. • In Section 1.2.1, add most up to date clinical data to support the changes of patient population in BM expansion. • In Section 1.3.1, Section 1.5, Section 6.6.1.3 and Section 8.1, add neurological

exam as one of the efficacy parameter for LM.

- In Protocol Synopsis, Section 1.3.1, Section 1.5 and Section 4.3, clarify the potential further expansion of the LM expansion cohorts to up to approximately 40 patients is for each drug respectively.
- In Protocol Synopsis, Section 1.3.1, Section 1.5, Section 4.3 and Section 8.2, add that the BM expansion cohorts for each drug may be further expanded to up to approximately 30 patients, respectively in order to confirm the safety and anti-tumour efficacy of AZD3759/AZD9291 in a larger group of patients.
- In Section 1.5, add the possibility to investigate a lower dose if the selected dose for AZD3759 LM/BM expansion based on the data from Part A is observed to be not well tolerated.
- In Section 1.3.1, Section 1.5 and Section 3.1, revise the patient population in Part B-BM expansion to "patients who have not received any EGFR TKI and have asymptomatic brain metastasis, either found during screening process which does not require local treatment in the opinion of the investigator or local treatment has been given (surgery or radiation), patient must be stable without corticosteroid and/or anti-convulsants treatment for at least 2 weeks before study enrolment" based on the emerging data in Part A.
- In Section 2 and Section 8, change Overall Survival from exploratory objective to secondary objective.
- In Section 3.2, add "Prior history of whole brain radiotherapy" as an exclusion criteria for AZD3759 BM expansion cohort(s).
- In Section 3.3 and 4.1, remove the fasting requirement for AZD9291 cohort(s) according to the most current IB of AZD9291.
- In Section 3.3 and 4.3.2, revise the fasting time window for AZD3759 cohorts to "≥2 hours prior to taking a dose to ≥1 hour post dose" according to the comments from US FDA.
- In Section 3.3.1, add the instructions about the concomitant use of localized palliative radiotherapy.
- In Section 4.1, add the instructions about missing a schedule dose for AZD3759/AZD9291.
- In Section 4.2.1, update dose escalation scheme to reflect the actual dose levels investigated in Part A.

- In Section 5.1, changes made to keep consistency with other sections.
- In Section 6.2.3, add details about the work on dECG collection and analysis.
- In Section 6.3.1, add full PK blood sampling 0-12 hours on C3D1 from patients in AZD3759 LM expansion and BM expansion cohorts in order to understand the PK profile observed so far and characterise the accumulation for both parent and metabolite.
- In Section 6.5.1, correct the total volume of CSF collection from BM patients to keep consistency with Section 6.3.1 and Section 6.4.1.3.
- In Section 8.2, revise the TV and LRV based on the changes to the patient population in BM and emerging data in LM. Remove futility check. Update the sample size of Part B based on the estimated number of expansion cohorts and estimated number of patients within each cohort.
- In Section 8.5, add details about the prospectively planned concentration-QTcF analysis.
- In Section 8.7, refine the analysis set in Table 12.

Version 3.0, [redacted]

Changes to the protocol are summarised below,

The key revision in Amendment 2 was to add overall survival as an exploratory objective for Part B, narrow down the inclusion criteria for BM expansions to be more focused on the target population, update the schedule of some assessments for better safety monitoring, allow more flexibility in this Phase I trial and also make some corrections and clarifications.

- In protocol synopsis, Sections 1.3.1, 1.5 and 4.3, add potential further LM expansion in order to confirm the safety and anti-tumour efficacy of AZD3759/AZD9291 in a larger group of patients.
- In Section 1.5, revise the description of patients in BM expansions to keep consistency with Section 3.1.
- In Sections 1.2.2 and 1.3.1, update the clinical data of AZD9291 according to the latest IB.
- In Section 1.3.1, further clarify the rationale of starting dose selection for AZD3759.

- In Section 1.4.2, revise the ECG assessment schedule of AZD3759 cohorts to keep consistency with Section 6.2.3, and revise the ECG and Echocardiogram/MUGA scan assessment schedule of AZD9291 cohorts to better monitor cardiac risk.
- In Section 2.3, add Overall Survival as an exploratory objective for Part B.
- In Sections 3.1 and 3.2, narrow down the inclusion criteria for BM expansions in order to focus on the target population. Clarify the eligibility criteria regarding prior treatment and known intracranial haemorrhage.
- In Section 4.2.1, clarify Table 1 shows the provisional dose escalation scheme, and additional dose level or dosing regimen might be added.
- In Section 4.2.1, add exceptions to the requirement of "no intra-patient dose escalations of AZD3759" to allow patients who have shown disease progression on AZD3759 and who may potentially benefit from a higher dose of AZD3759 to dose escalate if agreed by SRC.
- In Section 4.4, specify that tumour response assessment should be continued until disease progression intracranially if study treatment continues on the patients with disease progression extracranially but improved/stable intracranial disease.
- In Section 5.1, revise Table 4 and 5 to reflect the changes made to Sections 5.4, 6.2.2, 6.2.3 and 6.2.5.2.
- In Section 5.2, clarify the screening period is up to 28 days prior to first dosing.
- In Section 5.4, add survival follow up for patients in expansion cohorts.
- In Section 6.2.2, revise the vital signs schedule of AZD9291 cohorts for better safety monitoring.
- In Section 6.2.3, revise the ECG assessment schedule and add central digital ECG analysis requirement for AZD9291 cohorts and potentially for AZD3759 cohorts to better monitor cardiac risk.
- In Section 6.2.5.2, revise the assessment schedule of Echocardiogram or MUGA scan for AZD9291 cohorts to better monitor cardiac risk.
- In Section 6.3.1, increase the time window of PK samples taken at pre-dose to make it feasible. Add that additional blood and/or CSF PK samples may be collected to monitor potential drug-drug interactions.
- In Section 6.4.1.3, further clarify the purpose for 4mL CSF sample collection and add that "if for certain reasons some patients may not participate in CSF PoM and/or POP study, the agreement should be reached between site and AstraZeneca

before the patient receives the first dosing" to allow flexibility.

- In Section 6.5.1, add that "additional blood/CSF samples may be taken for further exploratory analysis if consent has been obtained from the patient" to allow flexibility as long as regulatory and/or ethics approvals are obtained.
- In Section 7.1.3, revise Table 10 to keep consistency with Section 5.4 where survival follow up is added for patients in expansion cohorts.
- In Section 7.3, correct the dose interruption criteria of Cystatin C and add flexible text for particular cases.
- In Section 8, specify the rationale of the sample size for further LM expansions, add Overall Survival as an end point for expansion cohorts, and refine the statistical part to ensure all analyses are correctly captured.
- Correct some typos throughout the protocol.

Version 2.0,

Changes to the protocol are summarised below.

Non-clinical data showed that AZD9291 could induce tumour regression in an EGFRm+ xenograft model implanted in the brain, suggesting AZD9291 has potential to have an effect on brain metastases (BM) and leptomeningeal disease (LM). In an ongoing phase I study of AZD9291 in patients with EGFR m+ non-small cell lung cancer (D5160C00001, AURA), there was anecdotal evidence (Kim D et al 2014) of BM shrinkage in a number of patients at doses 40–160 mg and RECIST evidence of BM non-target lesion stabilisation (non-CR/non-PD) at all doses tested. Thus the key revision in Amendment 1 was to include AZD9291 cohorts in patients with LM and/or BM in order to assess the anti-tumour efficacy, safety, pharmacokinetics and potential biological activity of AZD9291. The intention is to investigate AZD3759 and AZD9291 in the same patient population to define the safety, preliminary efficacy, pharmacokinetics and biomarkers associated with each compound. Therefore, all relevant information related to AZD9291 are incorporated into this amendment and the same patient inclusion/exclusion criteria will be applied to patient cohorts treated with AZD9291 as was previously applied to cohorts treated with AZD3759.

Other revisions include:

- In Sections 2.3 and 6.4.1.2, add genetic mutation analysis as one of the purposes for optional paired tumour biopsies
- In Section 3.1, clarify the inclusion criteria regarding previous radiotherapy in

patients with measurable BM

- In Sections 3.3 and 4.3.2, correct the fasting requirement from "fast ≥2 hours prior to taking a dose to ≥1 hour post dose" to "fast ≥1 hours prior to taking a dose to ≥2 hour post dose"
- In Sections 4.2.1 and 4.2.5, allow more than 6 evaluable patients being enrolled into each dose escalation cohort according to Bayesian design
- In Sections 5.1 and 6.4.1.1, mandate archival tumour sample collection (where available) for all patients to perform retrospective confirmation of the EGFR mutation status with a well validated EGFR mutation test
- In Sections 5.1, 6.4.1.5 and 6.7.3, remove cognitive testing from Part A (dose escalation) and urine KIM-1 analysis from the study to reduce the overall number of study related procedures
- In Sections 5.3, 6.2.2 and 6.6.1.2, add time window for study visit, CSF cytology and vital signs
- In Section 6.2.3, revise time window for ECG and the resting position based on logistical and operational considerations
- In Section 6.2.4, allow leukocyte differential to be either absolute values or percentage
- In Section 6.4.1.4, increase the volume of blood collected for blood borne biomarker analysis from 10ml to 20ml
- In Section 6.7.3, describe the Identification Task of cognitive test more accurately
- In Section 7.3.1, revise the dose interruption period of AZD3759 from 14 days to 21 days to allow more time for toxicity to recover based on experience in clinical studies of other drugs in the class.
- In Section 8.2, re-define sample size due to inclusion of AZD9291 cohorts
- In Section 8.8, add $AUC_{(0-12)}$ to statistical analysis
- In Appendix B, revise the causality assessment guideline for adverse events according to the new template
- In Appendix F, clarify the definition of measurable disease and non-measurable disease for brain metastasis
- Administrative changes, e.g. revise the numbering of sections and tables, correct

some typo, etc.

Version 1.0,
Initial creation

INTRODUCTION & STUDY FLOW CHART

A Phase I, Open-label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumour Activity of AZD3759 or AZD9291 in Patients with EGFR Mutation Positive Advanced Stage Non Small Cell Lung Cancer (NSCLC)

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer death worldwide. Genetic aberrations, such as Epidermal Growth Factor Receptor mutations (EGFR m+), have been identified as one of the key drivers of NSCLC tumour genesis. Since the discovery of EGFR mutations in 2004, it is now an accepted clinical consensus that NSCLC patients with tumours that have an EGFR sensitizing mutation are a distinct subset of NSCLC with respect to pathogenesis, prognosis, and treatment. There is a body of evidence demonstrating consistent efficacy of EGFR TKIs, such as gefitinib, erlotinib, and afatinib, in patients with sensitizing mutations compared to doublet chemotherapy. EGFR TKIs are established as the standard treatment for this subset of patients and are recommended by major treatment guidelines worldwide.

However, increasing incidence of central nervous system (CNS) metastasis (~40%), including leptomeningeal metastasis (LM) and brain metastasis (BM), has been reported, in particular post EGFR TKI treatment in EGFR mutant NSCLC. This may be associated with the improvement of imaging technology and routine screening (Barajas R et al 2012; Nguyen N et al 2013) and effective EGFR TKI treatment. The hypothesis behind this phenomenon is that due to limited blood brain barrier (BBB) penetration of current EGFR inhibitors (i.e. 1st-generation EGFR TKIs such as gefitinib, erlotinib or icotinib and 2nd-generation TKIs e.g. afatinib), these drugs can neither effectively treat CNS metastasis nor prevent development of CNS metastasis (Gow C et al 2008; Jackman D et al 2006). For patients with symptomatic BM, radiation therapy is the only Standard of Care (SoC) (Gow C et al 2008), and there is no approved molecular targeted therapy for the treatment/prevention of NSCLC CNS metastasis. Patients with asymptomatic brain metastasis had a shorter duration of PFS (median PFS of 6 months) compared to the overall patient population (median PFS of around 10 months) with 1st line EGFR TKI treatment (Wu Y et al 2013). A retrospective analysis reported that patients who carry EGFR sensitizing mutations and who have developed leptomeningeal metastases had a median overall survival of 7-11 months, compared to patients without leptomeningeal disease (median overall survival more than 20 months) (Umemura S et al 2012, Mok T et al 2009). Hence, there is an emerging unmet medical need to discover and develop a new agent, which could effectively cross the BBB.

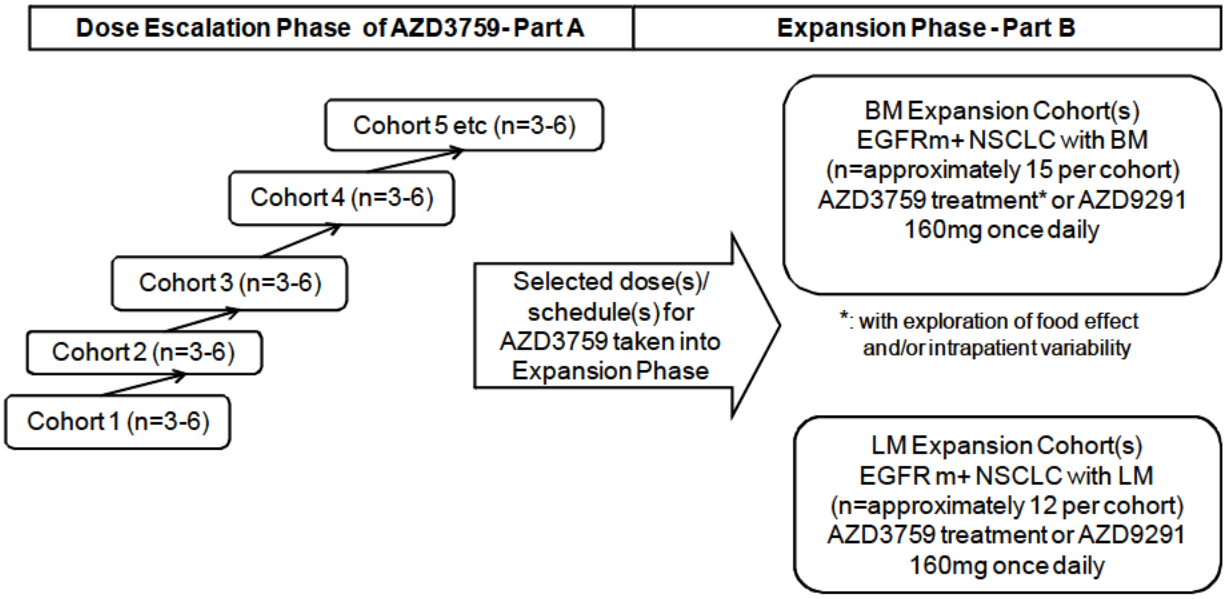
AZD3759 is a potent, oral, reversible inhibitor of EGFR with single mutation positive (EGFR m+, Tyrosine Kinase Inhibitor [TKI] - sensitivity conferring mutations, mainly L858R and Exon19Del). AZD3759 can achieve equivalent free exposure in the blood, brain and cerebrospinal fluid (CSF) in animal models. Through blocking EGFR phosphorylation and its downstream signalling pathways, AZD3759 achieved profound tumour growth inhibition in xenograft models implanted both subcutaneously and in the brain/leptomeninges, and significantly prolonged animal survival in these models. In addition, AZD3759 was also designed to improve the therapeutic margin between wild type and mutant EGFR of current EGFR inhibitors in order to minimize wild type EGFR related toxicity, such as skin rash and diarrhoea.

In this first time in patient study, AZD3759 will be administered to patients with advanced stage EGFR m+ NSCLC who have progressed following prior therapy at a starting dose of 50 mg twice daily, and will be escalated to reach a maximum tolerated dose (MTD) if possible. A twice-daily dose of an oral formulation of AZD3759 will be used initially, as deemed optimal and effective in non-clinical studies, primarily to determine the safety and tolerability of AZD3759 in patients with advanced stage EGFR m+ NSCLC who have progressed following prior therapy. Other schedules, including once daily and/or intermittent schedules, may be explored. Pharmacokinetics of AZD3759 and potential biological activity will also be investigated. Additional patients with LM and BM will be enrolled to expansion cohorts to further explore the safety and anti-tumour efficacy of AZD3759 at selected dose(s) as agreed by Safety Review Committee (SRC). In a BM expansion cohort (s), a preliminary investigation of the effect of food on exposure and/or intra-patient variability of the pharmacokinetics of a single dose will be made.

AZD9291 is an oral, potent, irreversible EGFR-TKI selective for sensitising (EGFRm+) and T790M resistance mutations. Preclinical studies indicate that AZD9291 has significant exposure in the brain and activity against EGFR m+ brain metastasis. In addition, anti-tumour activities of AZD9291 in patients with advanced stage EGFR m+ NSCLC including patients with brain metastasis have been reported in an ongoing Phase I study (D5160C00001, AURA). This compound has a good therapeutic margin between wild type and mutant EGFRs, and thus reported frequencies of wild type toxicities in the AURA study compare favourably with earlier generation EGFR-TKIs such as gefitinib. Therefore, in this study, patients with LM and BM may also be enrolled to assess the anti-tumour efficacy, safety, pharmacokinetics and potential biological activity of AZD9291.

Some cohorts in dose expansion may not be opened or terminated early in light of emerging data.

Study flow chart



Note: The LM expansion cohorts for each drug may be further expanded to up to approximately 40 patients, respectively in order to confirm the safety and anti-tumour efficacy of AZD3759/AZD9291 in a larger group of patients. The BM expansion cohorts for each drug may be further expanded to up to approximately 30 patients, respectively in order to confirm the safety and anti-tumour efficacy of AZD3759/AZD9291 in a larger group of patients.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
BBB	Blood Brain Barrier
BM	Brain Metastasis
BICR	Blinded Independent Central Review
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC(0-t)	Area under plasma concentration-time curve from zero to time t [amount·time/volume]
ctDNA	Circulating tumour deoxyribonucleic acid
CL/F	Total body clearance of drug from plasma after an oral dose
CLss/F	Total body clearance of drug from plasma after an oral dose at steady state
Cmax	Maximum plasma concentration
Cmax, ss	Maximum (peak) steady state drug concentration in plasma during dosing interval [amount/volume]
Cmin	Minimum plasma concentration
Cmin, ss	Minimum (trough) steady state drug concentration in plasma during dosing interval [amount/volume]
CNS	Central Nervous System
CR	Complete response
CRF	Case report form (electronic/paper)
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off date
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology group

Abbreviation or special term	Explanation
EGFR	Epidermal growth factor receptor
EGFR m+	Epidermal growth factor receptor single activating mutation positive
EORTC	European Organisation for Research and Treatment of Cancer
GCP	Good Clinical Practice
HNSTD	Highest non-seriously toxic dose
HRQoL	Health Related Quality of Life
IATA	International Air Transport Association
IB	Investigators brochure
IP	Investigational Product
ICH	International Committee on Harmonisation
LANO	Response Assessment for Neuro Oncology adapted for Leptomeningeal Metastasis
LM	Leptomeningeal Metastasis
MAD	Multiple ascending dose
MABEL	Minimally anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NE	Not evaluable
NOEL	No observed effect level
NSCLC	Non Small Cell Lung Cancer
NTL	Non-target lesion
OAE	Other significant adverse event
pAKT	phosphorylated AKT
PAD	Pharmacologically active dose
PD	Progression of disease
pEGFR	phosphorylated EGFR
pERK	phosphorylated ERK
PFS	Progression free survival
PHB	Personalised Healthcare and Biomarker group
PK	Pharmacokinetics

Abbreviation or special term	Explanation
POM	Proof of Mechanism
POP	Proof of Principle
PR	Partial response
PRO	Patient Reported Outcomes
QCP	Quantitative Clinical Pharmacology
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
SAD	Single ascending dose
SAE	Serious adverse event (see definition in Section 6.4.2)
SD	Stable disease
SRC	Safety review committee
STD10	Severely toxic dose in 10% of rodents
t½	Half-life
TKI	Tyrosine kinase inhibitor
tmax	Time to maximum plasma concentration
tmax ss	Time to maximum plasma concentration at steady state
TL	Target lesion
ULN	Upper limit of normal
Vss/F	Volume of distribution (apparent) at steady state after an oral dose
WBDC	Web based data capture
WBRT	Whoel brain radiotherapy
WHO	World Health Organisation

1. STUDY OBJECTIVES

1.1 Primary objective

To investigate the safety and tolerability of AZD3759 (both Part A and Part B) when given orally to patients with advanced stage EGFR m+ Non Small Cell Lung Cancer (NSCLC) who have progressed following prior therapy, including Maximum Tolerated Dose (MTD) determination, if possible (Part A only).

1.2 Secondary objective(s)

To determine the pharmacokinetics of AZD3759 and the N-demethylated metabolite in plasma following both single and multiple oral dosing.

To determine the pharmacokinetics of AZD3759 and the N-demethylated metabolite in urine following multiple oral dosing (Part A only).

To determine the pharmacokinetics of AZD3759 and N-demethylated metabolite in CSF following multiple oral dosing (only for patients with BM and/or LM).

To evaluate if AZD3759 affects 4b-hydroxy cholesterol which is an endogenous marker of CYP enzyme induction (Part B-BM expansion only).

To evaluate the effect of food on the pharmacokinetics of a single dose of AZD3759 in plasma (Part B-BM expansion only)

To evaluate anti-tumour efficacy in patients treated with AZD3759.

To determine the overall survival of BM and LM patients in Part B.

To evaluate anti-tumour efficacy and safety in patients treated with AZD9291 (only for patients with LM and/or BM).

To determine the pharmacokinetics of AZD9291 and metabolites in blood and CSF following multiple oral dosing (only for patients with LM and/or BM).

To evaluate the changes from baseline in CNS symptoms (analysed from BN20) in patients with LM treated with AZD3759/AZD9291.

1.3 Exploratory objective(s)

To investigate the presence, and/or identity of the drug metabolites of AZD3759.

To evaluate intra-patient variability of the pharmacokinetics of a single dose of AZD3759 in plasma (Part B-BM expansion only)

To investigate the effect of AZD3759/AZD9291 on the inhibition of Proof of Mechanism biomarkers (to include, but not limited to EGFR phosphorylation (pEGFR)) in optional tumour biopsies and in cell pellets from pre- and post-treatment CSF samples (in patients with LM).

To evaluate genetic mutations in archival tumour samples (e.g. diagnostic biopsy samples), optional fresh tumour biopsies, blood ctDNA and CSF samples (in patients with BM and/or LM) including but not limited to EGFR mutations that may be predictive of the activity of AZD3759/AZD9291.

To evaluate the changes from baseline in CSF biochemistry (in patients with LM) to support the demonstration of the anti-tumour effect of AZD3759/AZD9291 in addition to CSF cytology.

To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD3759/AZD9291 treatment and/or susceptibility to AZD3759/AZD9291.

To evaluate the changes from baseline in symptoms and QOL as measured by PROs (QLQ-C30, QLQ-BN20 and cognitive testing).

To explore potential correlation between relevant efficacy measures, biomarkers or safety variables and plasma or CSF concentration of AZD3759 (or N-demethylated Metabolite) and AZD9291 (or metabolites) and develop models to describe relevant relations.

To evaluate the best LM BICR assessment for AZD9291 LM patients (and if directed by the Sponsor, AZD3759 LM patients) according to LANO criteria.

2. BACKGROUND

2.1 Investigational agent

2.1.1 AZD3759

AZD3759 is a potent, oral, reversible inhibitor of epidermal growth factor receptor (EGFR) with single activating mutation positive (EGFR m+, Tyrosine Kinase Inhibitor [TKI] - sensitivity conferring mutations, mainly L858R and Exon19Del), with improved penetration of the blood brain barrier (BBB) and improved selectivity between wild type and mutant EGFRs, compared with current approved EGFR TKIs.

With the launch of EGFR TKIs, such as gefitinib and erlotinib, ~70% of patients with EGFR m+ (mainly L858R and Exon19Del) benefit from the treatment (Mok T et al 2009). However, current approved EGFR TKIs have limited ability to cross the BBB, and thus they could neither effectively treat patients with central nervous system (CNS) metastases nor prevent the development of CNS metastases (Grommes C et al 2011). AZD3759 was designed to improve

on the BBB penetration of current EGFR TKIs, and it can achieve equivalent free exposure in the brain, cerebrospinal fluid (CSF) and blood.

The most common adverse effects of current EGFR TKIs are skin rash and diarrhoea, which are related to inhibition of wild type EGFR activity. AZD3759 was designed to improve the selectivity between wild type and mutant EGFR, and preclinical data showed that it decreased the incidence and severity of skin rash and diarrhoea in rats and dogs.

Further details are provided in the Investigator Brochure.

2.1.2 AZD9291

AZD9291 is a potent, oral, irreversible inhibitor of both the single EGFRm+ (TKI-sensitivity confering mutation) and dual EGFRm+/T790M+ (TKI-resistance confering mutation) receptor forms of EGFR with a wide margin of selectivity against EGFR wild-type. AZD9291 has been approved in the US to treat patients with metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. In a rat quantitative whole body autoradiography (QWBA) study, high and persistent radioactivity was detected in the brain. In a mouse brain metastasis model, AZD9291 showed dose-dependent anti-tumor effect. Moreover, an ongoing Phase I study of AZD9291 (D5160C00001, AURA) demonstrated tumour responses in patients with brain metastasis.

2.2 Non-clinical and clinical information and correlative studies

2.2.1 Non-clinical and clinical information of AZD3759

In vitro studies showed that AZD3759 was potent against isolated wild type and mutant EGFRs with IC50 < 1 nM. *In vitro* cell-based PD assays showed that AZD3759 selectively inhibited phosphorylated EGFR (pEGFR) in cells with single EGFR mutations (IC50 < 10 nM), versus cells with wild type EGFR (IC50 > 50 nM). In mouse models with EGFR m+ tumour cells implanted subcutaneously (SC), in leptomeninges and in the brain, respectively, AZD3759 induced profound tumour regression at the doses equivalent to predicted human efficacious doses. In contrast, AZD3759 was less active in mouse model with wild type EGFR tumour cells implanted subcutaneously. The anti-tumour efficacy of AZD3759 was supported by positive correlation between pharmacokinetics and modulation of pEGFR, pAKT and pERK in the above models.

AZD3759 has high passive permeability and is not a substrate of the BBB efflux transporters P-gp and BCRP. *In vitro* studies indicated that CYP3A4 and CYP3A5 were the principal cytochrome P450 enzymes responsible for human metabolism, and thus DDI liability with CYP 3A4/5 inducer or inhibitor is considered likely. On the other hand, AZD3759 is unlikely to cause clinically significant DDI through inhibition or induction of cytochrome P450 enzyme activity. *In vivo* pharmacokinetic exposure of AZD3759 was demonstrated in a dose-proportional manner with equivalent free exposure in the blood, brain and CSF in rats. There was no significant accumulation on multiple daily dosing in rats and dogs. Micro dosing PET scan in monkeys showed that AZD3759 was distributed homogenously in monkey brain.

The key findings in the safety pharmacology studies were as following:

- In a secondary pharmacodynamics screen of 183 molecular targets, AZD3759 had significant activity (a defined IC_{50} value) at 40 targets.
- AZD3759 inhibited the function of the hERG channel with IC_{50} value of 13.3 μM using a manual patch clamping technique. Using automated patch clamping, AZD3759 showed activity at two other cardiac ion channels: hCav1.2/β2/α2δ (IC50= 29.2 μM) and hCav3.2 (IC_{50}= 98.8 μM).
- There were no notable effects on the cardiovascular system in dogs following administration of single doses up to 20mg/kg AZD3759.
- There was a small but statistically significant decrease in rectal temperature following administration of 400 mg/kg AZD3759. There were no other significant effects on CNS parameters observed.
- There were no notable effects on the respiratory system in rats following administration of single doses up to 400mg/kg AZD3759.

The key findings in the toxicity studies were as following:

- In both rat and dog toxicology evaluations almost all the observations and findings are consistent with consequences of the pharmacological inhibition of EGFR by AZD3759 or sequelae secondary to primary effects. A wide range of organs and tissues containing epithelial cell lineages were affected with changes spanning mild epithelial atrophy through to degenerative erosions, inflammation and necrosis. Dose limiting toxicity was principally deterioration of the animals from body weight loss as a consequence of gastrointestinal (GI) toxicity resulting from extreme effects of EGFR inhibition by AZD3759.
- In the rat 14 day MTD study and 1 month DRF studies there are a range of effects resulting from inhibition of EGFR including skin rash, eye secretion, diarrhoea, with associated histopathological effects extending up to inflammation and erosions in the GI tract and scab formation and inflammation/hair follicle necrosis of skin. When extreme, the GI effects were considered to represent dose limiting toxicity. Also observed were alterations to plasma chemistry and haematological WBC effects likely to be a consequence of inflammatory changes in the skin and gastric mucosa. Other key changes included depletion of cells in a number of lymphoid organs and evidence of renal toxicity illustrated by changes in plasma biomarkers and papillary necrosis and tubular degeneration.
- The 1-month rat GLP toxicity study evaluated doses up to 17 and 34 mg/kg/day (females and males respectively). There were many similar changes compared to the MTD and DRF studies. The range of epithelial tissues effects was extensive at

the higher doses and notably more severe in some organs like the GI tract. Biomarkers of renal toxicity were seen in both plasma and urinary evaluations and at the higher doses were associated with papillary necrosis and degeneration. At the end of the 4-week recovery period almost all the findings were absent indicating clear reversibility. The exceptions were some occasional observations of harderian gland necrosis, renal papillary necrosis (under recovery) with associated degeneration/regeneration, and minimal necrosis of hair papillae/hair sheath cells and mild myeloid hyperplasia of sternum. Due to the presence of a low incidence of skin effects and urinary blood biomarkers in males from low dose group, a NOEL was not established for male in this study, but for female NOEL was 3.4 mg/kg.

- In the MTD and 14 day repeat dose DRF study in the dog there was clear evidence of toxicity resulting from the pharmacology of EGFR inhibition. In the MTD phase acute doses of 80 and 125 mg/kg were not well tolerated and associated with decreased body weight and food consumption, marked clinical signs and GI disturbance, ocular effects and early termination due to deteriorating condition. Histopathological changes were observed included skin, GI, Kidney (papillary necrosis), inflammation of the ocular limbus and atrophy of the corneal epithelium. The MTD over 6 days was 30 mg/kg/day. In the 14-day DRF phase doses up to 20 mg/kg/day produced decreased body weight, food consumption, GI disturbance, ocular changes and increased WBC parameters likely to be due to epithelial inflammation. Corneal atrophy and limbus inflammation was seen at doses of 10 and 20 mg/kg/day and minor effects on food consumption and body weight at the low dose of 5 mg/kg/day.

- The 1-month dog GLP toxicity study evaluated doses up to 15 mg/kg/day. All doses were well tolerated although reduced body weight and food consumption was seen at the high dose. GI disturbance was present at 10 and 15 mg/kg/day. Minor changes in clinical chemistry were seen in the high and mid dose group. Increased WBC parameters were confined to the high dose. Histopathological changes were seen in the high dose in the skin (perifolliculitis) and eye (corneal epithelial atrophy). The NOEL was 2.5 mg/kg/day and at the end of the 4-week recovery period all changes were absent indicating complete recovery.

- There were no findings to indicate the potential for genotoxicity when AZD3759 was assessed in the *in vitro* Ames and Mouse Lymphoma assays and in the *in vivo* Rat Micronucleus study.

- AZD3759 was considered to be weakly phototoxic in the in vitro 3T3 assay. However, the IC50 for in vitro phototoxicity (35.3 μM) was 2000-fold higher than likely human plasma exposure (19.7 nM), hence AZD3759 was not considered to present a significant phototoxic hazard to man.

- The results from the toxicology studies support progression into clinical trials in patients with advanced cancer, including NSCLC and brain metastatic conditions.

Further details are provided in the Investigator Brochure.

Where AZD3759 has been administered to patients as part of study D6030C00001, common adverse events have included skin effects (such as rash and dry skin) and diarrhea. These have mainly been CTCAE Grade 1. AZD3759 achieved Ctrough free plasma and CSF exposure above pEGFR IC50 of EGFRm+ cells at the doses ≥ 100 mg BID. In 4 patients with leptomeningeal metastases evaluable for PoM assessment, 3 out of 4 had > 50% pEGFR inhibition in CSF tumor cells after one week treatment with AZD3759 at the doses of 50 mg, 200 mg and 300 mg BID. More than 50% tumor cell number decrease was also observed in 4 out of 5 patients with leptomeningeal metastases. As of 30 December 2015, among the 24 patients with measurable extracranial lesions and evaluable for RECIST assessment, 9 (3 out of 9 switched immediately after progression from EGFR TKIs) had tumour shrinkage extracranially, suggesting that AZD3759 was active against tumours outside the brain. Among the 20 patients with measurable BM and evaluable for RECIST assessment, 8 (3 out of 8 switched immediately after progression from EGFR TKIs) had tumour shrinkage in the brain, indicating that AZD3759 was active against tumours in the brain.

2.2.2 Non-clinical and clinical information of AZD9291

In vitro cellular EGFR phosphorylation assays demonstrated potent inhibition of single-activated (EGFRm+) and double-T790M mutant (EGFRm+/T790M) assays, and much weaker inhibition towards wild-type EGFR was observed. *In vitro* wash-out and time dependent cellular kinetic studies demonstrated an irreversible mechanism of action of AZD9291. Oral treatment of mice bearing EGFRm+ and EGFRm+/T790M xenograft tumours subcutaneously lead to profound tumour growth regression. In contrast, higher doses of AZD9291 were required to achieve significant tumour growth inhibition in wild-type EGFR xenograft models. Xenograft growth regression with AZD9291was accompanied by dose and time-dependent pharmacodynamic inhibition of phospho-EGFR (p-EGFR) and the key downstream biomarkers phospho-Akt (p-Akt) and phospho-Erk (p-Erk) across mutant and wild-type EGFR disease models *in vivo*. The active metabolites of AZD9291, AZ5104 and AZ7550, showed similar pharmacological selectivity and activity profiles to parent, although AZ5104 showed a smaller margin of selectivity against wild-type EGFR *in vitro*.

In the tissue distribution studies for both partially-pigmented and albino rats, the central nervous system (ie, brain and spinal cord) contained quantifiable radioactivity up to 21 days post-dose, suggesting that AZD9291 drug-related radioactivity may have crossed the BBB to some degree.

In the preclinical toxicology programme gastrointestinal toxicity was the principal dose-limiting finding in rats and dogs (mainly evident as body weight loss and reductions in food consumption, along with emesis and soft/fluid faeces in dogs), but eye lesions (corneal epithelial ulceration/erosion) were also a factor in the 1 month dog study. Testicular pathology (seminiferous tubular atrophy/degeneration and/or spermatid retention) and secondary epididymal findings were seen in the 1 month rat (no observable effect level (NOEL) at 4 mg/kg/day) and dog studies (no NOEL identified). These findings were not present following 1 month off-dose. AZD9291 was not mutagenic in the Ames test or in the mouse lymphoma

assay, and was not clastogenic in the *in vivo* rat micronucleus test. AZD9291 was not phototoxic in an *in vitro* phototoxicity (3T3 cell) assay.

Recent data showed that AZD9291 dosed once daily orally led to significant tumour regression at both doses of 5mg/kg and 25mg/kg in a brain metastasis (BM) model, which is established by injection of PC-9_Luc cell line through intra-internal carotid artery (ICA). The bioluminescence signals were measured by IVIS Xenogen imaging system to monitor the tumour growth. In particular, the higher dose of 25 mg/kg achieved a more durable and sustained tumour inhibition. In addition, AZD9291 significantly prolonged animal survival in BM model. The improvement of animal survival by 5 and 25mg/kg AZD9291 was statistically significant with 63-83% and 78% 8 weeks survival rate respectively.

As of 16 January 2015, approximately 945 subjects have been exposed to treatment with AZD9291 at dose levels range from 20 mg to 240 mg, with exposure ranging from 1 to 609 days. This includes 45 healthy volunteers who have received AZD9291 20 mg as single dose. Overall subject exposure includes 518 subjects that participated in Phase I studies, 411 subjects that participated in the Phase II programme and 23 subjects that participated in the Phase III programme.

Data from Study D5160C00001 (AURA) in pre-treated patients with centrally-tested EGFR T790M mutation positive tumours; investigator assessed analyses, showed that treatment with AZD9291 resulted in tumour shrinkage with an investigator-assessed ORR of 58.6% across all doses. In pre-treated patients with centrally-tested EGFR T790M mutation positive tumours at the 80 mg dose level, investigator-assessed and BICR (Blinded Independent Central Review) assessed results were similar: investigator-assessed ORR was 65.6% (95% CI: 52.3, 77.3) and BICR assessed ORR was 54.2% (95% CI: 40.8, 67.3). In pre-treated patients with centrally-tested EGFR T790M mutation negative tumours; investigator assessed analyses, the ORR was 23.2% (95% CI: 13.9, 34.9) in 16 of 69 evaluable for response patients. PFS was 2.8 months (95% CI 2.1, 4.2) in patients with centrally confirmed T790M mutation negative NSCLC. Responses were durable, with the BICR-assessed median duration of response for the 80 mg dose in patients whose tumours were T790M mutation positive calculated as 12.4 months. BICR-assessed preliminary median PFS was 13.5 months (95% CI: 8.3, NC) in patients with centrally tested T790M mutation positive NSCLC (38% maturity). In treatment naïve patients with an evaluable response, the ORR (confirmed and awaiting confirmation) by RECIST v1.1 was 63% (26/41; 95% CI 47, 78). The disease control rate (CR + PR + stable disease) was 95% (39/41; 95% CI 83, 99). There were an insufficient number of progression events to determine the PFS rate. As AURA was primarily designed as a first-time-in-man study, intensive assessment of BM responses was not in the scope of the study, and baseline magnetic resonance imaging (MRI) scan was not mandated for all patients. However, there was anecdotal evidence of BM shrinkage in a number of patients (at doses 40–160 mg), and RECIST evidence of BM non-target lesion stabilisation (non-CR/non-PD) at all doses tested (Kim D et al 2014).

AZD9291 was well tolerated at all dose levels tested (20 to 240 mg daily) in the Phase I component of the AURA study, and as such, a non-tolerated dose has not been defined. The

most common adverse events (AEs) have been diarrhoea, rash (grouped term), paronychia and dry skin. Most of these events have been of mild to moderate intensity. Across the AURA and AURA2 studies, and including 1 fatal AE reported after the DCO date of 16 January 2015, a total of 18 deaths have been attributed to fatal AEs; of these, only 4 fatal AEs have been considered causally related to AZD9291 treatment by the Investigator; these comprise 3 patients with AEs of interstitial lung disease (ILD) and 1 patient with an AE of sepsis/pneumonia/lung cancer. Two of the 3 ILD events were considered to be the primary cause of death (although subsequent autopsy data for 1 of these patients states that the primary cause of death was lung cancer); for the remaining case, death was considered as due to both disease under study and the AE of ILD. No other treatment-related fatal AEs have been reported in any other studies in the AZD9291 clinical programme. The most commonly reported SAEs were as expected in a population of patients with advanced NSCLC. The most common SAEs were pneumonia, pulmonary embolism, pleural effusion and pneumonitis. SAEs that were considered as being possibly related to study drug included: pneumonitis, ILD, diarrhoea, decreased appetite, pulmonary embolism and thrombocytopenia. The most common AE leading to discontinuation was pneumonitis. Note that permanent discontinuation was a protocol requirement for all confirmed ILD-like cases.

Further details are provided in the Investigators' Brochure.

3. STUDY DESIGN AND RATIONALE

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a phase I, open-label, multicentre study of AZD3759 or AZD9291 administered orally in patients with advanced stage EGFR m+ NSCLC. The study design allows an escalation of dose of AZD3759 with intensive safety monitoring to ensure the safety of the patients.

There are two parts to this study. Part A, Dose escalation (AZD3759) and Part B, Dose expansions (AZD3759 and AZD9291, respectively).

Part A, Dose escalation (AZD3759)

Approximately 30 evaluable patients with advanced stage EGFR m+ NSCLC will be enrolled in Part A of this study. The total number of patients will depend upon the number of dose escalations necessary. Fewer or more patients may be required if additional schedules are explored or if agreed by SRC. All patients enrolled into this part should have progressed on treatment with a single-agent EGFR TKI and doublet or single agent chemotherapy.

Each dose escalation cohort will comprise of a minimum of 3 evaluable patients and a maximum of 6 evaluable patients (using Bayesian Adaptive Design - see Section 5.1.1 for

more details). It is planned to recruit at least 2 patients with measurable BM per dose cohort (final decision to reside with SRC).

Eligible patients will receive a single dose of AZD3759 (Cycle 0) followed by at least 48 hours washout. Multiple twice daily dosing will commence on Cycle 1, Day 1 for 21 days (other schedules, including once daily dosing and intermittent schedules, may be explored). At the end of 21 day multiple dosing, patients may continue to receive AZD3759 at the discretion of the investigator until disease progression or until they experience unmanageable drug related toxicity, as long as they are continuing to derive clinical benefit. In the first cohort, administration of the first dose will be separated from the start of dosing of the subsequent patients by at least 7 days for the first patient. Dosing frequency, washout duration, and timing of PK and safety assessments may be adjusted during the study on the basis of emerging safety and pharmacokinetic data.

For patients without LM, clinical efficacy will be based on tumour scans conducted every 6 weeks until progression according to modified RECIST 1.1 (Section 6.8.1.1).

Additional patients may be recruited and receive the MTD or an effective dose as agreed by SRC to further ascertain the safety profile and pharmacokinetics of AZD3759. These patients will receive AZD3759 for 21 days (Cycle 1 Day 1-21). At the end of 21 days dosing patients may continue to receive AZD3759 at the discretion of the investigator until disease progression or until they experience unmanageable drug related toxicity, as long as they are continuing to derive clinical benefit.

Patients with LM may be recruited during Part A into the highest dose level which is defined as tolerated and predicted to be efficacious at the time the patient becomes available to enter the study, and will be assessed for DLTs. To aid definition of Proof of Mechanism, if patients with LM are recruited, CSF samples will be collected pre/post treatment for pharmacokinetic and biomarker analysis. For patients with LM, clinical efficacy will be based on assessment of CSF cytology (performed at Cycle 1 Day 8 and every 6 weeks until disease progression), neurological exam, and brain and/or spinal MRI scans (performed every 6 weeks until disease progression), and supported by assessment of CNS symptom improvement.

Part B, Dose expansion

This study will open expansion cohorts in patients with LM or BM, respectively, to further evaluate the efficacy, safety, tolerability, pharmacokinetics and biological activity of AZD3759 in specific patient sub groups at dose(s) to be agreed by the SRC. Approximately 2 expansion cohorts per metastasis type will be enrolled.

Part B also includes an investigation of the effect of food on exposure as well as intra-patient variability in BM expansion.

In addition, patients with LM or BM may also be enrolled in order to assess the anti-tumour efficacy, safety, pharmacokinetics and potential biological activity of AZD9291.

Some cohorts in dose expansion may not be opened or early terminated in light of emerging data.

LM expansion

Patients with progressive intracranial disease, but stable extracranial disease will be enrolled to the LM expansion cohort(s) (EGFR TKI treatment naïve patients need not have stable extracranial disease). Eligible patients (approximately n=12 per cohort) will receive AZD3759 twice daily dosing (other schedules, including once daily and intermittent schedules, may be explored) at the selected dose level of AZD3759 or AZD9291 160mg once daily until disease progression (investigator judgement) or until they experience unmanageable drug related toxicity, as long as they are continuing to derive clinical benefit. If the selected dose of AZD3759 from Part A is not tolerated in the LM expansion, a lower dose would be investigated. Within AZD9291 LM expansion cohort, a sub-cohort of T790M+ LM patients will be enrolled.

To aid definition of Proof of Mechanism, CSF samples will be collected pre/post treatment for pharmacokinetic and biomarker analysis.

Clinical efficacy will be based on assessment of CSF cytology (performed at Cycle 1 Day 8 (AZD3759 cohorts) or Cycle 2 Day 1 (AZD9291 cohorts) and every 6 weeks until disease progression), neurological exam, and assessment of brain and/or spinal MRI scans (performed every 6 weeks until disease progression), and supported by assessment of CNS symptom improvement.

BM expansion

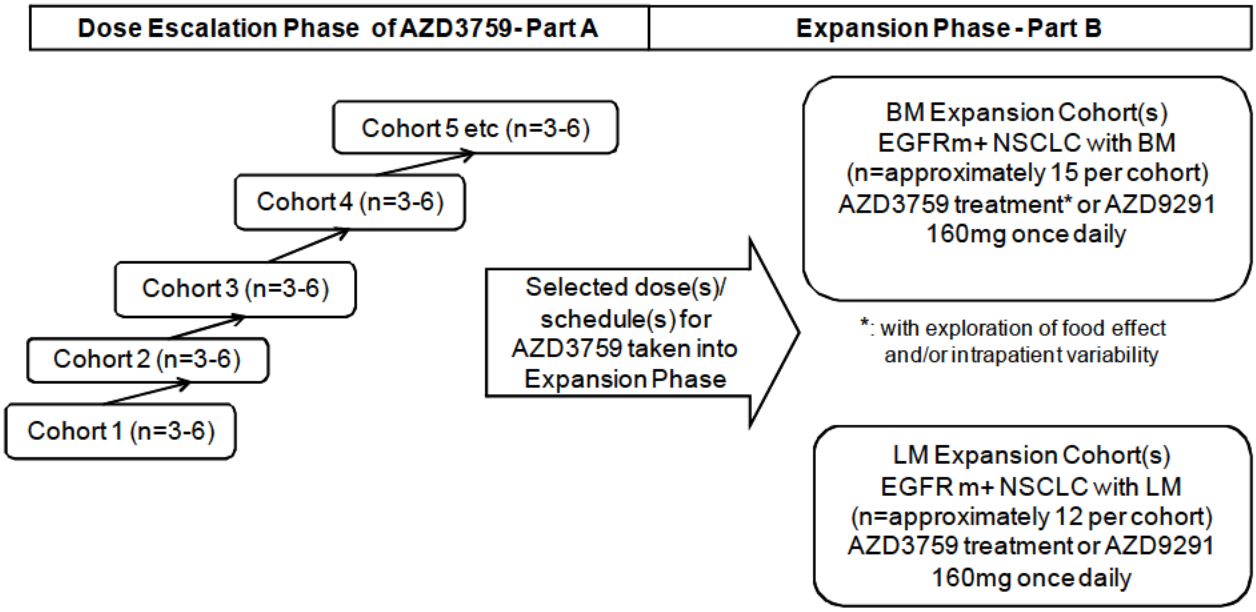
Patients who have not received any EGFR TKI and have asymptomatic brain metastasis will be enrolled to the BM expansion cohort(s). Eligible patients (approximately n=15 per cohort) will receive AZD3759 multiple twice daily dosing (other schedules, including once daily and intermittent schedules, may be explored) at the selected dose level of AZD3759 or AZD9291 160mg once daily until objective disease progression by RECIST or until they experience unmanageable drug related toxicity, as long as they are continuing to derive clinical benefit. If the selected dose of AZD3759 from Part A is not tolerated in the BM expansion, a lower dose would be investigated.

Within an AZD3759 arm, the effect of food will be investigated in one BM expansion cohort. Patients will be randomised to receive single doses of AZD3759 on Days 1 and 4 of Cycle 0 in a fasted or fed (medium fat meal) condition at an agreed dose. Continuous dosing will start on Day 1, Cycle 1 at the dose agreed for the expansion phase. Intra-patient variability will be investigated in another BM expansion cohort if two BM cohorts are enrolled. Patients will receive single doses of AZD3759 on Days 1 and 4 of Cycle 0 in a fasted condition at an agreed dose.

CSF samples will be collected post treatment for pharmacokinetic analysis.

Clinical efficacy will be based on tumour scans conducted every 6 weeks, with patients being treated until progression according to modified RECIST 1.1, i.e. separate assessment of extracranial disease and brain metastasis.

Figure 1 Study flow chart



Note: The LM expansion cohorts for each drug may be further expanded to up to approximately 40 patients, respectively in order to confirm the safety and anti-tumour efficacy of AZD3759/AZD9291 in a larger group of patients. The BM expansion cohorts for each drug may be further expanded to up to approximately 30 patients, respectively in order to confirm the safety and anti-tumour efficacy of AZD3759/AZD9291 in a larger group of patients.

3.2 Rationale for conducting this study and for study design

Rationale for conducting this study

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer death worldwide. Genetic aberrations, such as Epidermal Growth Factor Receptor mutations (EGFR m+), have been identified as one of the key drivers of NSCLC tumourigenesis. Since the discovery of EGFR mutations in 2004, it is now an accepted clinical consensus that NSCLC patients with tumours that have an EGFR sensitizing mutation are a distinct subset of NSCLC with respect to pathogenesis, prognosis, and treatment. There is a body of evidence demonstrating consistent efficacy of EGFR TKIs, such as gefitinib, erlotinib, and afatinib, in patients with sensitizing mutations compared to doublet chemotherapy. EGFR TKIs are established as the standard treatment for this subset of patients and are recommended by major treatment guidelines worldwide.

However, increasing incidence of central nervous system (CNS) metastasis (~40%), including leptomeningeal metastasis (LM) and brain metastasis (BM), has been reported, in particular

post EGFR TKI treatment in EGFR mutant NSCLC. This may be associated with the improvement of imaging technology and routine screening (Barajas R et al 2012; Nguyen N et al 2013) and effective EGFR TKI treatment. The hypothesis behind this phenomenon is that due to limited blood brain barrier (BBB) penetration of current EGFR inhibitors (i.e. 1st-generation EGFR TKIs such as gefitinib, erlotinib or icotinib and 2nd-generation TKIs e.g. afatinib), these drugs can neither effectively treat CNS metastasis nor prevent development of CNS metastasis (Grommes C et al 2011; Jackman D et al 2006). For patients with symptomatic BM, radiation therapy is the only Standard of Care (SoC) (Gow C et al 2008), and there is no approved molecular targeted therapy for the treatment/prevention of NSCLC CNS metastasis. Patients with asymptomatic brain metastasis had a shorter duration of PFS (median PFS of 6 months) compared to the overall patient population (median PFS of around 10 months) with 1st line EGFR TKI treatment (Wu Y et al 2013). A retrospective analysis reported that patients who carry EGFR sensitizing mutations and who have developed leptomeningeal metastases had a median overall survival of 7-11 months, compared to patients without leptomeningeal disease (median overall survival more than 20 months) (Umemura S et al 2012, Mok T et al 2009). Therefore, with improved penetration of the BBB, AZD3759 has the potential to provide clinical benefit to patients with NSCLC with CNS metastases, including leptomeningeal and brain metastases.

This is a first time in patient study primarily designed to evaluate the safety and tolerability of AZD3759 at ascending doses in patients with EGFR m+ NSCLC, who progressed following prior therapy with an EGFR TKI agent, followed by expansions of the cohorts at selected dose level(s) in patients with LM and BM, respectively. This study will also characterize the pharmacokinetics of AZD3759 in blood and CSF, and explore potential biological activity. With improved selectivity between wild type EGFR and mutant EGFR in pre-clinical studies, AZD3759 is anticipated to have less wild type EGFR related toxicity, such as skin rash and diarrhoea, than current EGFR TKIs (i.e. 1st generation EGFR TKIs such as gefitinib, erlotinib or icotinib and 2nd generation TKIs e.g. afatinib) in human. The results from this study will form the basis for decisions on future studies.

With the emerging data of AZD9291 in pre-clinical animal models and the Phase I study, AZD9291 cohorts in patients with LM and BM, respectively, will also be added in this study in order to assess the anti-tumour efficacy, safety, pharmacokinetics and potential biological activity of AZD9291.

Rationale for study design

Study design

This first time in patient study aims to address safety and preliminary anti-tumour efficacy in patients with advanced stage EGFR m+ NSCLC with or without CNS metastases. In Part A, patients with 3rd line or above EGFR m+ NSCLC who have progressed following an EGFR TKI agent and chemotherapy will be recruited for evaluation of safety of AZD3759, since there is no standard treatment available for this group of patients. In Part B, patients with EGFR m+ NSCLC who have leptomeningeal disease or who are EGFR TKI treatment naïve BM patients will be enrolled into the expansion of LM and BM cohort(s), respectively, to

further assess safety and anti-tumour efficacy at selected dose(s) of AZD3759 (patients with LM may be EGFR TKI treatment naïve if an efficacy signal has been seen in Part A). The rationale of enrolling EGFR TKI treatment naïve BM patients is based on the emerging data in Part A (Section 2.2.1). Patients with LM post-EGFR TKI must have stable extracranial disease to ensure that their extracranial disease is still sensitive to EGFR TKIs to enable evaluation of duration of response (and to avoid potentially confounding the study outcome due to extracranial progression). In addition, patients with LM and BM may also be enrolled in order to assess the anti-tumour efficacy, safety, pharmacokinetics and potential biological activity of AZD9291. Within AZD9291 LM expansion cohort, a sub-cohort of T790M+ LM patients will be enrolled.

This study will use a Bayesian adaptive design approach to dose escalation to improve the efficiency and precision of the MTD estimation compared to a traditional 3+3 design (Sweeting M et al 2013). Dose escalation decisions will be made on a minimum of 3 patients.

The 21-day assessment period was selected, as the major toxicities leading to cessation of dose escalation in such studies tend to occur within 21 days. As this is the first administration of an agent in humans, in the first cohort the administration of the first dose is separated by at least 7 days for the first 2 patients. This will ensure that any acute toxic effects of the administration will have sufficient time to be identified before additional patients are exposed. There will be a minimum of 2 days between completion of dosing of Cycle 1, in the last required evaluable patient from one cohort and the start of dosing in the subsequent cohort in order for the SRC meeting to be called, and minutes of the dose escalation decisions to be distributed to all participating sites**.**

Exploratory objectives

AstraZeneca will collect samples to allow investigation of the presence and identity of metabolites of AZD3759.

As part of the clinical drug development programme for AZD3759 and AZD9291, AstraZeneca plans to include investigations into variations in exploratory biomarker profiles and their relationship to drug effect. These biomarkers may be derived from DNA, ribonucleic acids (RNA), proteins and/or metabolites. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from treatment, explain outliers or non-responders, explain adverse reactions related to drug exposure, or evaluate potential resistance mechanisms. This research may result in an understanding of the impact of variation between individuals and how it can be utilised to bring better drugs to the clinic. Collection of CSF samples from patients with LM and optional tumour biopsies are also planned in this study to investigate the effect of AZD3759/AZD9291 on the inhibition of Proof of Mechanism biomarkers (to include, but not limited to EGFR phosphorylation (pEGFR)). The ability to acquire appropriate consent to collect biological samples is important to establish an archive and allow future meta-analysis of data derived across studies with AZD3759/AZD9291.

AstraZeneca intends to perform genetic research in the AZD3759/AZD9291 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD3759/AZD9291 which may result in improvements in the design and interpretation of future clinical studies and potentially the development of genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD3759/AZD9291 but also susceptibility to NSCLC for which AZD3759/AZD9291 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to AZD3759/AZD9291 susceptibility and drug action.

Patient reported outcomes (PRO) and cognitive test data will also be collected to explore disease-related symptoms and health related quality of life (HRQoL).

4. PATIENT SELECTION AND RESTRICTIONS

Investigators should keep a record, i.e., patient screening log, of patients who entered pre-study screening.

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of starting study treatment. Under no circumstances can there be exceptions to this rule.

Patients with LM (with or without BM) will be assessed as a patient with LM in Part A, and included in LM cohort(s) in Part B.

Patients with measurable BM but without LM will be assessed as a patient with BM in Part A, and included in BM cohort(s) in Part B.

4.1 Inclusion criteria

For inclusion in the study, patients must fulfil all of the following criteria.

1. Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses. For inclusion in optional genetic and/or biomarker research, patients must provide informed consent for the research.

2. Male or female aged at least 18 years. Aged at least 20 if Japanese.

3. Histologically or cytologically confirmed diagnosis of NSCLC with single activating EGFR mutations (L858R or Exon19Del). EGFR mutation status should have been determined at local labs that are CLIA-certified laboratories in the US (if US sites participate in this study); in other countries, the EGFR mutation status

should have been determined locally using a well-validated and robust methodology which has been approved by the regulatory authority.

4. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 3 months. For patients with LM, ECOG performance status 0 to 2 is acceptable.

5. Females should agree to use adequate contraceptive measures (as defined in Section 4.3), 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

   – Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

   – Women under 50 years old would be considered postmenopausal if they have been amenorrhoeic for at least 12 months following the cessation of exogenous hormonal treatments, and have serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in the postmenopausal range for the institution.

6. Male patients should be willing to use barrier contraception, i.e., condoms, until 3 months after last study drug is taken.

7. Willing to remain in hospital from Cycle 0 Day 1 up to at least completion of Cycle 1 Day 21 (Japanese patients in Part A only).

8. In Part A, patient must have had prior treatment with at least one line of a single agent EGFR TKI (eg, gefitinib, erlotinib, afatinib, or AZD9291) and at least 1 line of chemotherapy (doublet or single agent) and progressed either intracranially or extracranially. For patients with intracranial progression, prior radiation therapy is not mandatory.

9. In Part B-BM expansion, patients must have not received any EGFR TKI and have asymptomatic brain metastasis, either found during screening process which does not require local treatment in the opinion of the investigator or local treatment has been given (surgery or radiation), patient must be stable without corticosteroid and/or anti-convulsants treatment for at least 2 weeks before study enrollment

10. In Part B-LM expansion, patients who received previous EGFR TKI treatment must have stable extracranial disease. EGFR TKI treatment naïve patients can also be enrolled into AZD9291 cohorts, or AZD3759 cohorts if efficacy signal has been seen in Part A and agreed by SRC (No new patients are planned to be enrolled into

AZD9291 cohort via this criteria in 2016, but will be enrolled by criteria #15 instead).

11. For patients with neither LM nor measurable BM (Part A): At least one measurable extracranial lesion not previously irradiated or biopsied within the screening period, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

12. For patients with LM (both Part A and Part B): Confirmed diagnosis of LM by positive CSF cytology. Diagnosis by MRI only is not eligible for study entry.

13. For patients with LM (both Part A and Part B): At least one site of CNS leptomeningeal disease that can be assessed by magnetic resonance imaging (MRI) and which is suitable for repeat assessments. Measurable CNS or extracranial disease is not required.

14. For patients with measurable BM but without LM (both Part A and Part B): At least one measurable intracranial lesion that, if previously irradiated, has progressed or not responded to radiation therapy, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter by magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. Measurable extracranial disease is not required.

15. In Part **B-AZD9291 LM expansion (sub-cohort of T790M+ LM patients)**, patients must have central confirmation of T790M+ mutation status from a sample taken after documented progression on the last treatment administered prior to enrolling in the study. Patients must have received prior therapy with an EGFR TKI and may also have received additional lines of treatment. Stable extracranial disease is not required.

4.2 Exclusion criteria

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

1. Intervention with any of the following:

   - Any investigational agents or study drugs from a previous clinical study within 30 days of the first dose of study treatment
   - Treatment with an EGFR TKI (e.g., erlotinib or gefitinib) within 8 days or approximately 5 x half-life, whichever is the longer, of the first dose of study treatment (if sufficient wash-out time has not occurred due to schedule or PK properties, an alternative appropriate wash-out time based on known duration

and time to reversibility of drug related adverse events could be agreed upon by AstraZeneca and the Investigator)

- Any cytotoxic chemotherapy or other anticancer drugs for the treatment of advanced NSCLC from a previous treatment regimen within 14 days of the first dose of study treatment.
- Major surgery procedure (excluding placement of vascular access), or significant traumatic injury within 4 weeks of the first dose of study treatment, or have an anticipated need for major surgery during the study
- Radiotherapy with a wide field of radiation within 4 weeks or radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment with the exception of patients receiving radiation to more than 30% of the bone marrow which must be completed within 4 weeks of the first dose of study treatment.
- Prior history of whole brain radiotherapy (only applicable for AZD3759 BM expansion)
- Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of AZD3759/AZD9291) medications or herbal supplements known to be potent inhibitors or inducers of CYP3A4/5 and potential inhibitors of CYP2C8 (for patients to be enrolled into AZD9291 cohorts only). Patients currently receiving steroids will not be excluded from the study except for patients in AZD3759 BM expansion (Appendix G).

2. Any unresolved toxicities from prior therapy, greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 1 at the time of starting study treatment with the exception of alopecia.

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

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 patient to participate in the trial or which would jeopardise compliance with the protocol. Screening for chronic conditions is not required.

5. Positive Hepatitis B surface antigen (HbsAg) or positive HCV antibodies or confirmed positive HIV test result (Section 6.3.6.3).

6. Any of the following cardiac criteria:

- Mean resting corrected QT interval (QTc) > 470 msec obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine derived QTc value.
- Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG, e.g., complete left bundle branch block, third degree heart block, and second-degree heart block.
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, any concomitant medication known to prolong the QT interval, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives

7. 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 > 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 > 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. Total bilirubin >3 times the ULN in patients with documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or in the presence of liver metastases
   - Creatinine >1.5 times ULN concurrent with creatinine clearance < 50 mL/min (measured or calculated by Cockcroft and Gault equation). See Section 7.3. Confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN.
   - If bone metastases are present and liver function is otherwise considered adequate by the investigator then elevated ALP will not exclude the patient.

8. History of hypersensitivity to active or inactive excipients of AZD3759/AZD9291 or drugs with a similar chemical structure or class to AZD3759/AZD9291

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

10. Known intracranial haemorrhage which is unrelated to tumour

11. Significant medical or psychiatric illness that would interfere with compliance and ability to tolerate treatment as outlined in the protocol

12. Refractory nausea and vomiting if not controlled by supportive therapy, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of AZD3759/AZD9291

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

14. **For patients with LM and/or BM**, CNS complications that require urgent neurosurgical intervention (e.g. resection or shunt placement).

15. **For patient with LM**, inability to undergo collection of CSF, either by repeated lumbar puncture or placement of an Omaya reservoir.

In addition, the following are considered criteria for exclusion from the exploratory genetic research:

16. Previous allogeneic bone marrow transplant

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

4.3 Restrictions

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

1. Female patients of child-bearing potential should use reliable methods of contraception from the time of screening until 3 months after discontinuing study 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.

2. Female patients should not breast-feed during the trial.

3. Male patients 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. Patients should avoid procreation for 3 months after completion of trial treatment. Patients should refrain from donating sperm from the start of dosing until 3 months

after discontinuing study treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

4. For patients in AZD9291 cohort (s), study drug can be taken with or without food at the same time of each day. For patients in AZD3759 cohort s, except for the planned fed doses (in Part B-BM expansion) arm, patients should fast (water only) for ≥2 hours prior to taking a dose to ≥1 hour post dose. The tablets should be swallowed whole with water. Following a review of the PK data for food effect in the food effect cohort, the SRC may decide to remove the fasting restriction for AZD3759 cohorts (except for visits when PK samples will be taken).

5. Patients 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 AZD3759/AZD9291 until at least one week after symptoms have resolved. If a patient 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 AZD3759/AZD9291 is permanently discontinued. Patients 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 AZD3759/AZD9291 has been permanently discontinued. Patient should consult the clinic promptly if they have any concerns.

For restrictions relating to concomitant medications see Section 5.1.2.1.

4.3.1 Concomitant treatments

Guidance on medicines to avoid, medications that require close monitoring and on washout periods based on potential interactions with AZD3759 and AZD9291 are provided in Appendix G.

Other anticancer agents, investigational agents and radiotherapy should not be given while the patient receiving study treatment. The patient may be allowed to take localized palliative radiotherapy if it has been confirmed that there is no disease progression on the local lesion. Brain radiotherapy is not allowed. Study drug interruption is not required in the case of local palliative radiotherapy for pain control (excluding chest). For local palliative radiotherapy to chest, study drug should be interrupted during and up to 7 days post the palliative radiotherapy.

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 Sponsor Study Physician.

Patients may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases.

Other medication, other than those described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

5. STUDY TREATMENT AND CONDUCT

5.1 Treatment

AZD3759 will be administered twice daily (dosing interval is 12 hours). Alternative frequencies or intermittent schedules may be instigated in response to emerging safety, tolerability or PK data. If a patient misses taking a scheduled dose, within a window of 2 hours, it is acceptable to take the dose. If it is more than 2 hours after the dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their AZD3759, they should not make up for this dose, but should take the next scheduled dose.

AZD9291 will be administered once daily. Doses should be taken approximately 24 hours apart at the same time point each day. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their AZD9291, they should not make up for this dose, but should take the next scheduled dose.

Patients will receive either AZD3759 or AZD9291.

The investigational product AZD3759 (in the form of one or more of the following sizes: 10 mg/tablet, 50 mg/tablet and 100 mg/tablet) and AZD9291 (in the form of 80 mg/tablet) will be supplied by AstraZeneca as tablets for oral dosing. AZD9291 40mg tablets may also be supplied when available. Additional information about the investigational product may be found in the Investigator Brochure.

Tablets will be packed in bottles with child-resistant closures. One or more bottles of AZD3759 or AZD9291 will be dispensed at each dispensing visit depending on the dose. 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 study drug to a patient.

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The labels will fulfil Good Manufacturing Practice Annex 13 requirements for labelling. Label text will be translated into local language.

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

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

The subject will be given a leaflet or a card, which provides the address, telephone number of the main contact for the information on the product and the clinical trial. The subject will need to carry this card at all times.

The study will start with fasted dosing for AZD3759 cohorts, and will include an option to reassess the fasting status of AZD3759 after review of the PK data for food effects in the food effect cohort, as described in Section 6.5. For patients in AZD9291 cohort (s), study drug can be taken with or without food.

5.1.1 Starting dose and dose escalation scheme and stopping criteria

Dosing will begin at 50 mg twice daily. A cycle of study treatment will be defined as 21 days of continuous dosing.

In the first cohort, patient dosing will be staggered such that administration of the first dose is separated by at least 7 days for the first 2 patients. Providing there are no serious or unexplained safety issues, as determined by the SRC, dosing of the remainder of the cohort will continue as suitable patients are identified. However, should ambiguous findings occur, the SRC may choose to stagger the start of dosing for the remainder of the patients in the cohort. Providing there are no safety concerns after completion of the first cohort, subsequent cohorts of patients will be dosed as suitable patients are identified. If ambiguous findings occur after the first cohort the SRC may choose to stagger dosing in the second cohort and likewise for subsequent cohorts.

Patients will be enrolled to ensure a minimum of 3 and a maximum of 6 evaluable patients per cohort (except at MTD or an effective dose as agreed by SRC if additional patients are recruited, or if patients with LM are recruited into a tolerated dose level, or additional patients need to be enrolled as suggested by Bayesian design). Dose escalation and de-escalation will follow the Bayesian Adaptive Design scheme below:

- If no dose-limiting toxicity (DLT) at any dose has been observed, then dose escalation may occur without further modelling.
- After the first DLT has been observed (at any dose), a Bayesian Logistic Regression model will be used to inform subsequent dose selections. After each cohort, cumulative data on the evaluable patients will be used estimate the predicted probability of a DLT at each potential next dose. The recommendation for the next dose will be based on the following principles.
  - No dose may be chosen where the predicted probability of a DLT exceeds 50%.

  - The recommendation for the next dose will be chosen to minimise the variance of the final MTD (for definition see Section 5.1.3.1) estimate.
  - The number of evaluable patients at any dose is planned not exceed 6 (except at MTD or an effective dose as agreed by SRC if additional patients are recruited, or if patients with LM are recruited into a tolerated dose level, or additional patients need to be enrolled as suggested by Bayesian design).

- Dose escalation and de-escalation will be completed when any of the following occur:
  - The required precision of the estimated MTD is achieved (i.e. the ratio of the Upper/Lower 95% Credible Interval limits for the estimated MTD < 5.0)
  - The maximum absorbable dose is achieved (i.e. when no increase in exposure with increasing dose is observed and a change in scheduling is conducted)
  - The maximum number of evaluable patients for each dose cohort in part A has been reached.
  - Unfeasible number of tablets required to deliver dose and no anticipated improvement in efficacy with increasing dose
  - Decision made by SRC to stop the dose escalation part
- Prior estimates of doses at which 25% and 50% of patients experience DLTs will be used to inform the Bayesian model.
- Dose increases will be permitted after review of data from a minimum of 3 evaluable patients.
- Prior to a dose escalation decision the SRC will review all available safety and PK data.
- Escalations will not exceed doubling of the dose in principle. However, up to a quadrupling of dosing may be permitted in the first two escalations only, if the drug concentrations of the first or second level are not measurable or are deemed to be far from predicted drug exposure (e.g. greater than 2-fold difference) and there have been no significant safety or tolerability issues.

See Table 1 for provisional dose escalation scheme, however, all proposed dose escalation levels after the starting dose may be adjusted in light of emerging safety, tolerability and/or PK data and decided by the SRC**.**

Table 1 Provisional dose escalation scheme

Cohort	Dose mg (twice daily dosing) *
1	50

Table 1 Provisional dose escalation scheme

Cohort	Dose mg (twice daily dosing) *
2	100
3	200
4	300
5	500

* It is possible for additional dose levels or dosing regimens (e.g., qd) to be added during the course of the study.

There will be a minimum of 2 days between conduct of the last patient assessment required for the SRC review from one cohort and the start of dosing in the subsequent cohort.

There is no planned intra-patient dose escalations of AZD3759. Investigators identifying patients who have shown disease progression on AZD3759 and who may potentially benefit from a higher dose of AZD3759 should discuss the case with the study team physician. The decision to dose escalate and the appropriate dose will reside with the SRC and will be based on the individual. The patient may continue imaging assessment after dose escalation.

The dose for subsequent cohorts or a decision to stop recruitment to Part A of the study will be agreed by the SRC after review of the data from each cohort (see Section 5.1.5).

5.1.2 Dose expansion (Part B)

Part B will be conducted to refine the safety, tolerability and PK and biological activity of AZD3759 in patients with patient population participating in this part. Patients will be enrolled to ensure approximately 12 evaluable patients with LM per dose cohort and approximately 15 evaluable patients with BM per dose cohort. In addition, separate cohorts of approximately 12 evaluable patients with LM and approximately 15 evaluable patients with BM may be enrolled to receive AZD9291 160mg once daily. The LM expansion cohorts for each drug may be further expanded to up to approximately 40 patients, respectively in order to confirm the safety and anti-tumour efficacy of AZD3759/AZD9291 in a larger group of patients. The BM expansion cohorts for each drug may be further expanded to up to approximately 30 patients, respectively in order to confirm the safety and anti-tumour efficacy of AZD3759/AZD9291 in a larger group of patients.

Within the expansion phase safety will continue to be periodically reviewed by the SRC.

5.1.2.1 Treatment allocation in dose expansion phase

All patients will receive either the SRC agreed dose(s) of AZD3759 or 160 mg of AZD9291 in the expansion phase.

5.1.2.2 Preliminary food effect and intra-patient variability

One BM cohort in Part B will investigate the effect of food on AZD3759 phamacokinetics.

Patients will be randomized to receive single doses of AZD3759 on Days 1 and 4 of Cycle 0 in a fasted or fed (medium fat meal) condition at the dose agreed for the expansion phase. See details in Table 2. Continuous dosing will start on Day 1, Cycle 1 at the dose agreed for the expansion phase.

Table 2 Fasted/fed sequence

Sequence	Day 1 of Cycle 0	Day 4 of Cycle 0
1	Fasted	Fed
2	Fed	Fasted

In fasted condition, the morning dose will be given while fasted (≥2 hours prior to taking a dose to ≥1 hour post dose).

In fed condition, the morning dose will be after a meal on Days 1 and 4 of Cycle 0. Patients should start the recommended meal 30 minutes prior to administration of the drug product. Patients should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal of about 650 total calories consisting of around 30% fat, 54% carbohydrate and 17% protein. The drug product should be administered with 240 mL of water.

Intra-patient variability will be investigated in another BM expansion cohort if two BM cohorts are enrolled. Patients will receive single doses of AZD3759 on Days 1 and 4 of Cycle 0 in a fasted condition at agreed dose.

Pharmacokinetic samples will be taken throughout these days, as detailed in Section 6.5.1.

5.1.3 Definition of dose-limiting toxicity

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value that occurs from the first dose of study treatment (Day 1, Cycle 0) up to the last dose of Cycle 1 (21 days from the start of multiple dosing) assessed as unrelated to disease progression, intercurrent illness, or concomitant medications that despite optimal therapeutic intervention meets any of the following criteria:

1. Haematological toxicity that is:
   - ≥ CTCAE grade 4 present for more than 4 days
   - Febrile neutropenia
2. Non-haematological toxicity ≥ CTCAE grade 3 including:

- QTc prolongation (> 500 msec or 60msec above baseline)

3. Any other toxicity that:

   - Is greater than that at baseline, is clinically significant and/or unacceptable, and is judged to be a DLT by the SRC.
   - Is a protocol defined stopping criteria (see Section 5.1.6)
   - Results in a disruption of dosing schedule of more than 14 days

A DLT excludes:

4. Alopecia of any grade

5. Isolated laboratory changes of any grade without clinical sequelae or clinical significance

The incidence and type of DLT-type toxicity from Cycle 2 and beyond will be taken into account by the SRC in determining dose escalation steps.

5.1.3.1 Definition of maximum tolerated dose

The MTD is defined as the highest dose at which the predicted probability of a dose limiting toxicity (DLT) is less than 25%. Refer to Section 5.1.1 for detailed description of Bayesian Adaptive Design scheme.

5.1.4 Definition of evaluable patient

For decisions on dose escalation, an evaluable patient is defined as a patient that has received AZD3759 and either:

- has completed minimum safety evaluation requirements during the first 21 days of continuous dosing

or

- has experienced a DLT during the first 21 days of continuous dosing

5.1.5 Safety Review Committee

After each dose level during the dose escalation phase of the study, the SRC will evaluate the available safety, tolerability and pharmacokinetics of AZD3759 to decide the next dose.

The SRC will consist of:

- Sponsor Study Physician, who will chair the committee, or delegate
- Principal Investigator or delegate from each investigational site

In addition, other physicians from the following may be invited:

- Global Safety Physician or delegate
- Medical Science Director or delegate
- An independent external neuro-oncologist

The Clinical Pharmacology Scientist, Study Statistician, Patient Safety Scientist, and Study Leader may also be invited as appropriate. The Safety Review Committee Remit document for this study will define the exact membership and who should be present for decisions to be made.

Further internal or external experts may be consulted by the SRC as necessary.

Once there are at least 3 evaluable patients at a dose level the SRC will review and assess all available safety data from the cohort together with available PK data to make a decision on the dose for the next cohort of patients. Any dose interruptions and reductions will be taken into account. It is planned to conduct the SRC meeting on bi-weekly basis, but the frequency may be adjusted according to patient enrollment rate, emerging data, etc.

The decision may be to:

- Proceed with dose escalation – refer to Section 5.1.1
- Expand the cohort to a maximum of 6 evaluable patients (except at MTD or an effective dose as agreed by SRC if additional patients are recruited, or if patients with LM are recruited into a tolerated dose level, or additional patients need to be enrolled as suggested by Bayesian design)
- De-escalate the dose either to a previous lower dose level or to an intermediate lower dose level
- Stop the dose escalation part of the study
- Initiate dose expansion cohort(s)
- Evaluate alternative dosing frequencies/intermittent dose schedules
- Add additional patients at MTD

When there are other patients that are ongoing at the time of this review, the SRC may decide to defer their decision until these further patients become evaluable.

Any patient started on treatment in error, as he/she failed to comply with all of the selection criteria but meets the criteria of an evaluable patient, will be reviewed on a case by case basis

by the SRC to determine if the patients data should be included or excluded in the decision for dose escalation.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to the investigators prior to dosing any new patients.

5.1.6 Dose modifications

5.1.6.1 Toxicity management and dose modifications to AZD3759

If a patient experiences a CTCAE grade 3 and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. Patients with QTcF prolongation fulfilling the DLT criteria (i.e. confirmed QTcF prolongation to >500 msec absolute or a > 60 msec increase from baseline) should have study treatment interrupted and regular ECGs performed until resolution to baseline. If the QTc prolongation toxicity does not resolve to ≤ grade 1 within 21 days the patient will be permanently withdrawn from study treatment.

Patients with Cystatin C level above the ULN and creatinine values reaching CTCAE grade 3 will be permanently withdrawn from study treatment. Patients with Cystatin C level above the ULN and creatinine reaching CTCAE grade 2 should have study treatment interrupted until the values for Cystatin C return to normal and creatinine revert to ≤ CTCAE grade 1 and the patient is showing clinical benefit, treatment with AZD3759 may be restarted at the same dose or a lower dose. If the values for Cystatin C does not revert to normal and creatinine does not revert to ≤ CTCAE grade 1 after 21 days, then the patient should be withdrawn from the study and observed until resolution to baseline.

If any other toxicity resolves or reverts to ≤ CTCAE grade 2 within 21 days of onset and the patient is showing clinical benefit, treatment with AZD3759 may be restarted at the same dose or a lower dose using the rules below for dose modifications (see Figure 2) and agreement with the AstraZeneca Study Team Physician as needed.

If any other toxicity does not resolve to ≤ CTCAE grade 2 after 21 days, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

On resolution of toxicity within 21 days:

- If a further episode of the same AE subsequently requires dose interruption, AZD3759 must restart at one dose level lower (unless in Cohort 1, when restart will be at Cohort 1 dose) on resolution/improvement of the AE at the discretion of the Investigator.

- If a different AE subsequently requires dose interruption, AZD3759 may restart at the same or one dose level lower (unless in Cohort 1, when restart will be at Cohort 1 dose) on improvement of the AE at the discretion of the Investigator.

Patients who are at the lowest possible dose ie, who have their dose previously reduced to the Cohort 1 dose and who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.

For particular cases which don't follow the dose modification rules as defined in Figure 2, an agreement should be reached with the AstraZeneca Study Team Physician.

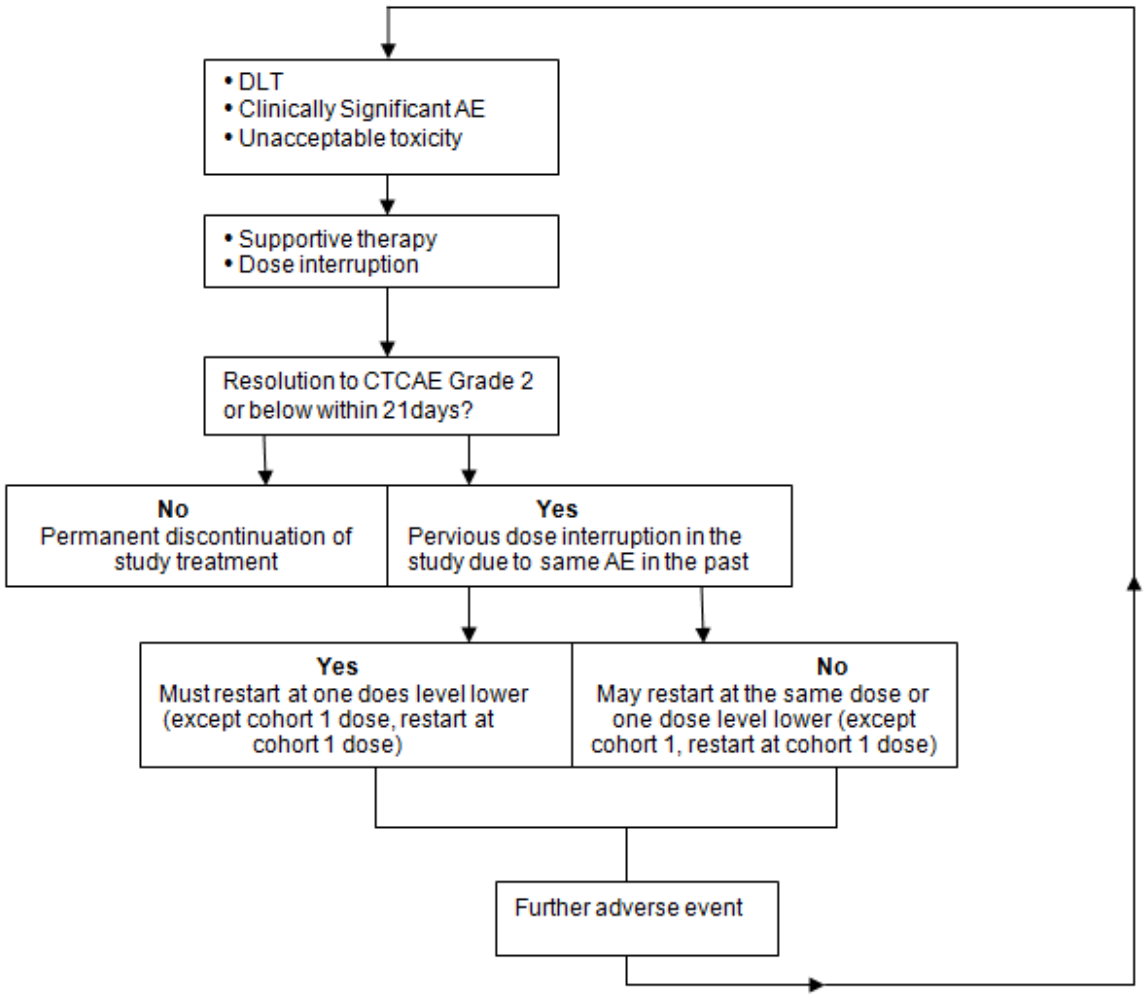
Patients experiencing corneal ulceration or Interstitial Lung Disease (ILD) will not be permitted to restart study treatment.

No within-patient dose re-escalation will be permitted. 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 should be informed. A questionnaire regarding the results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters, bronchoscopy with biopsy as needed) will be sent to Investigators. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema, or pulmonary haemorrhage. 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 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.

Assessment timings if dosing is interupted

If a patient misses any doses of AZD3759 during the 21-day evaluation period of Cycle 1, please contact the AstraZeneca Study Team for advice regarding the evaluability of the patient and appropriate timing of the PK assessments. All other assessments, including laboratory safety assessments, vital signs and RECIST should continue to be performed as per study plan, relative to the baseline assessments.

Figure 2 Dose modifications for toxicity related to AZD3759



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 AZD3759 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 may be taken of skin reactions.

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 AZD3759, will be provided to investigators.

5.1.6.2 Toxicity management and dose modifications to AZD9291

Treatment with AZD9291 should be temporarily interrupted if one of the following adverse events occurs despite optimal supportive care, when not attributable to the disease under investigation, where the Investigator considers the AE of concern to be specifically associated with AZD9291:

- Any intolerable adverse event regardless of grade
- Any adverse events ≥ CTCAE Grade 3 (despite optimal supportive care)
- Any DLT-type toxicity as defined in Section 5.1.3

Patients with QTcF prolongation (ie, confirmed QTcF prolongation to >500 msec absolute or a > 60 msec increase from baseline) should have study treatment interrupted and regular ECGs performed until resolution to baseline. If the QTc prolongation toxicity does not resolve to ≤ grade 1 within 21 days the patient will be permanently withdrawn from study treatment.

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

For any other toxicity, if the event resolves or reverts to ≤ CTCAE grade 2 within 21 days of onset, treatment with AZD9291 may be restarted at the same dose or a lower dose using the rules below for dose modifications (Table 3) 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 21 days, then the patient should be withdrawn from the study and observed until resolution of the toxicity.
- If a different AE or further episode of the same AE subsequently requires dose interruption, AZD9291 may restart at the same dose or a lower dose (unless already at 80 mg, when restart will be at 80 mg if 40 mg tablets are unavailable; or unless already at 40 mg, when restart will be at 40 mg if 40 mg tablets are available) on resolution/improvement of the AE at the discretion of the Investigator.

No within-patient dose re-escalation will be permitted in this study

Table 3 AZD9291 dose modifications

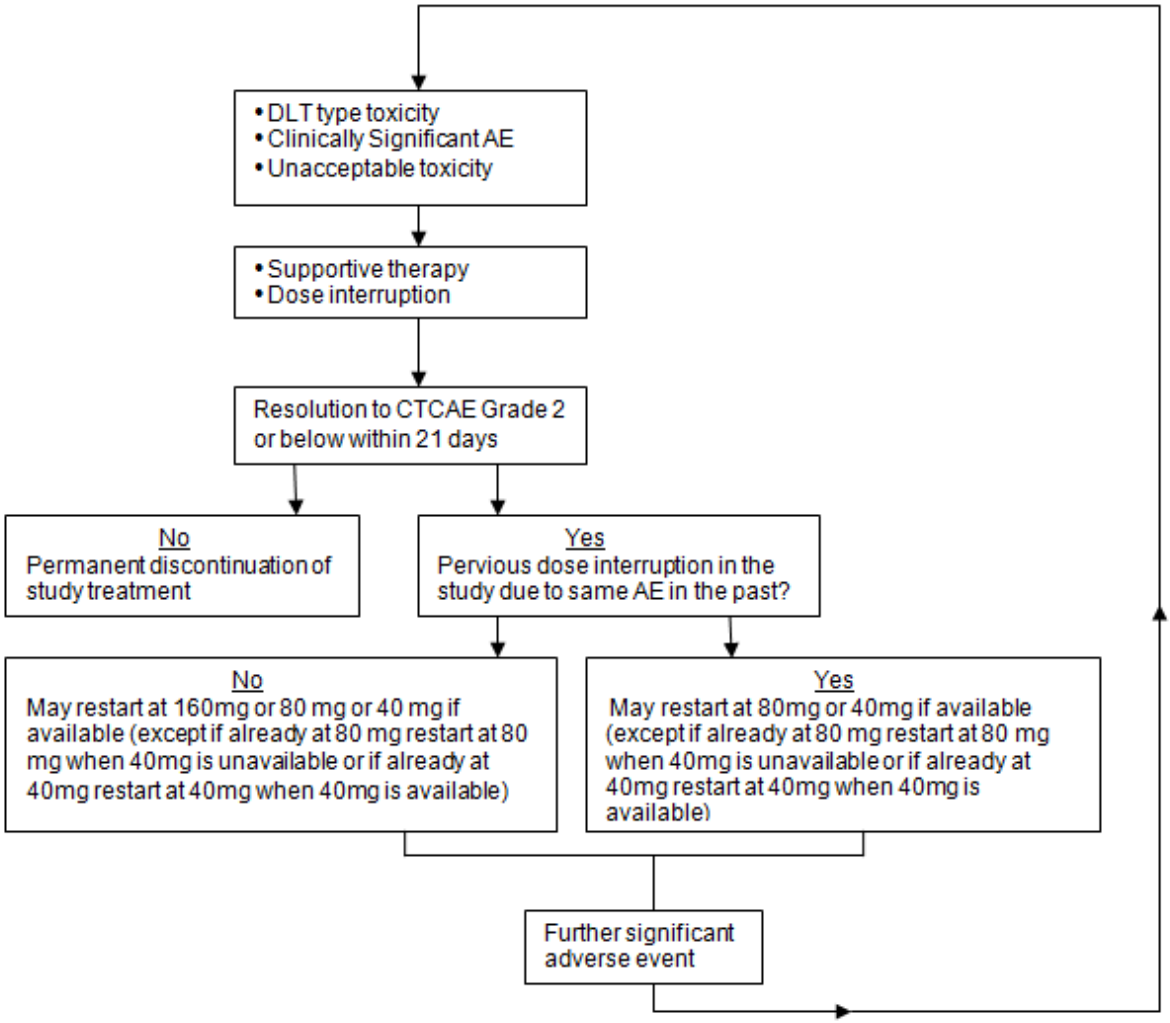
Dose at time of toxicity	Reduced dose level
160 mg OD	80mg OD
80 mg OD	No further reduction or 40mg OD if 40 mg tablets are supplied
40mg OD (if 40mg tablets available)	No further reduction

For particular cases which don't follow the dose modification rules as defined in Figure 3, an agreement should be reached with the AstraZeneca Study Team Physician.

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca study team should be informed. A questionnaire regarding the results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters) will be sent to Investigators. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment 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.

Figure 3 Dose modifications for toxicity related to AZD9291



5.1.7 Duration of therapy

Patients may continue to receive AZD3759/AZD9291 as long as they are continuing to show clinical benefit, as judged by the investigator and agreed by AZ study physician, and in the absence of meeting any of the discontinuation criteria.

5.1.8 Treatment compliance and accountability

The investigational product should only be used as directed in this protocol. Details of treatment with investigational product for each patient will be recorded in the Case Record Form.

Patients should return all unused medication and empty containers to the investigator.

The study personnel at the investigational site will account for all drugs dispensed and returned. Unless otherwise authorized by sponsor, all investigational product supplies unallocated or unused by the patients must be destroyed by procedures approved by sponsor or returned to sponsor or its designee.

5.2 Rationale for dose regimen, dose escalation scheme and stopping criteria

Starting dose of AZD3759

The predicted efficacious dose in human (approximately 100 mg twice daily) was based on non-clinical modeling of the human exposure which can continuously inhibit ≥50% pEGFR signals in EGFR mutation driven tumour cells; at the equivalent exposure in mice, tumour regression was observed in xenograft tumours implanted both subcutaneously and in the brain/leptomeninges.

The international guidance for starting dose selection for agents in cancer patients (ICH S9) recommends that the starting dose should be either $1/10^{th}$ of the severely toxic dose (STD10) in rodent toxicity studies or $1/6^{th}$ of the highest non-seriously toxic dose (HNSTD) observed in non-rodent studies. Based on the findings in non-clinical GLP tox studies, in which rats are defined as the most sensitive species, 34 mg/kg/day (STD for male rats) has been used in the calculation for human dose prediction. In dogs, the HNSTD was 15 mg/kg/day from the 1-month study. Using the conversion factors published on the FDA website (FDA Guidance 2005), the human equivalent dose (HED) derived from $1/10^{th}$ of the rat STD was calculated to be 33.6 mg/day, whilst the HED derived from $1/6^{th}$ of the dog HNSTD was calculated to be 81 mg/day. If the most conservative data were used, 33.6 mg/day would be the recommended starting dose according to this guidance. In the ICH S9 document this guidance is referred to as a commonly adopted calculation for a starting dose for many new anticancer therapies but does not state that this is a mandatory requirement. In addition, the ICH S9 document mentioned that “the goal of selecting the start dose is to identify a dose that is expected to have pharmacologic effects and is reasonably safe to use”.

First generation EGFR inhibitors such as gefitinib were developed before the issue of ICH S9 guidance and therefore would not be a valid anticancer drug with which to compare the first dose in human approach proposed for AZD3759. At the time of development of first generation EGFR inhibitors there was limited understanding of the pharmacological effects of these kinase inhibitors and, as would be expected, clinical oncologists chose starting doses carefully on the basis of findings in the non-clinical animal safety studies. At the current time of development of AZD3759 the scientific understanding of the non-clinical and clinical effects of EGFR inhibitors is much more comprehensively understood by the oncology medical and regulatory authority community. Additionally, there is significant knowledge and experience of the clinical management of pharmacologically related effects in cancer patient.

A dose of 50 mg twice daily is proposed as the starting dose in this first time in patient study in patients with EGFR m+ advanced NSCLC. This is around 3 times the ICH S9 recommended starting dose. The rationale for proposing 50 mg twice daily as the starting dose

are as follows: 1) The non-clinical GLP tox findings of AZD3759 are similar to other EGFR TKIs, such as gefitinib and AZD9291, with dose limiting toxicities related to inhibition of wild type EGFR; 2) The wild type EGFR related toxicities are consistently translatable from non-clinic to clinic across multiple EGFR TKIs; 3) Wild type EGFR related toxicities are typically monitorable, reversible and manageable and there is extensive clinical knowledge and experience of monitoring and managing these toxicities based on >5 years of use of EGFR TKIs in clinical practice; 4) Based on preclinical to clinical modelling, continuous coverage of pEGFR IC_{50} (0.0074μM) of EGFRm+ cells is anticipated to induce tumour regression in CNS metastases. At the starting dose of 50 mg twice daily (free C_{max} 0.01μM and free C_{min} 0.004μM), AZD3759 is predicted to cover pEGFR IC_{50} of EGFRm+ cells for about 20 hours, but not pEGFR IC_{50} in EGFR wild type cells. Therefore, the proposed 50 mg twice-daily starting dose is anticipated to start bringing benefit to patients with minimal risk of toxicities. With comprehensive monitoring and management of adverse events, the higher starting dose is expected to bring safe benefit to patients with minimal delay of dose escalation.

Dose of AZD9291

Mathematical simulations were performed by inputting clinical PK data into prior pre-clinical PKPD models of both single (PC9, EGFR m+) and double (H1975, EGFR m+/ T790M+) mutant lines. These simulations suggested that significant tumour growth inhibition would occur in tumours located outside the brain possessing both the sensitizing and resistance (T790M) mutations at clinical doses of 20 mg and above. In addition, this modelling suggests that there would be no further benefit of dosing above 80 mg; maximum tumour growth inhibition would be reached at a clinical dose of 80 mg for tumours outside the brain.

Additionally PK-PD modelling has also been used to simulate tumour growth inhibition in EGFR m+ NSCLC brain metastases (Kim D et al 2014). This indicated that at the 80 mg dose level, the lower 95% confidence interval would still achieve a 200% tumour growth inhibition (greater than 100% indicates tumour regressions), however at the 160 mg dose level a higher proportion of tumours would achieve the deepest tumour growth inhibition of 240%.

In study D5160C00001 (AURA) approximately dose-proportional increases in AZD9291 exposure were observed across the 20–240 mg dose range, so on average a 160 mg dose of AZD9291 will give double AZD9291 exposure compared to an 80 mg dose. Visual inspection of occurrence of rash and diarrhoea versus AZD9291 exposure in Study D5160C00001 suggests some relationship between exposure and occurrence of rash and/or diarrhoea.

Clinically the 160mg dose level for AZD9291 is eight fold higher than the minimum efficacious dose tested, and 66% of the maximum dose tested, 240mg, which had no DLTs during the 28-day DLT evaluation period. Anecdotal evidence of tumour shrinkage has been reported to date at the 160mg dose level. As of 2nd December 2014, the data in phase I component of AURA study showed that the frequency of adverse events (AE, Grade ≥3 AE, SAE) reported in the 160mg cohort were broadly similar to those occurring at 80 and 240mg. The frequency of Grade≥3 AE causally related to AZD9291 as assessed by investigator was higher in the 160mg cohort (28.8%) than at 80mg (13.6%) and 240mg (19.0%). The frequency of EGFR TKI type AEs was higher in the 160mg cohort than at the 80mg dose level:

diarrhoea 67.5% vs. 35.9%, rash 41.3% vs. 25.2%, dry skin 36.3% vs. 14.6% and paronychia 28.8% vs. 21.4% respectively. Investigators will already be familiar with the management of these class-related toxicities; however, additional recommendations for the management of toxicities seen on AZD9291 will be provided.

In summary the 160 mg dose has been chosen for this study as preclinical PK-PD modelling suggests that the increased AZD9291 exposure at 160mg compared to 80mg may increase the probability that tumours located in the brain have the deepest response and, whilst the AE frequency is higher at 160mg than at 80mg, the tolerability profile observed at 160mg is still considered to be manageable in this patient population.

Dose escalation scheme

The dose escalation scheme will not exceed doubling of the dose, in principle. However, up to a quadrupling of the dose may be permitted in the first two escalations in light of emerging data, which will be discussed and decided in Safety Review Committee (SRC) meeting. This will ensure that the fewest possible cohorts are exposed to AZD3759 below the presumed therapeutic dose. If the safety and tolerability profile of a cohort is considered to be equivocal by the SRC, a further cohort of additional patients may be enrolled at that dose schedule before a dose escalation decision is made. Non-clinical modelling provides only an approximate prediction of human pharmacokinetics, therefore the planned dose escalation scheme and/or frequency of dosing and/or treatment schedule may be amended in light of emerging data.

Expansion cohorts

In Part B, expansion cohorts will be initiated in the EGFR m+ NSCLC population with LM (n=approximately 12 per cohort) and BM (n=approximately 15 per cohort) at defined dose level (s), to further evaluate the safety, pharmacokinetic and anti-tumour efficacy of AZD3759 and AZD9291 as monotherapy, respectively. The doses of AZD3759 taken forward to Part B will be defined by the SRC. It is expected that AZD3759 at therapeutic doses and AZD9291 at 160mg once daily will demonstrate a clinically significant effect on CSF cytology, neurological function, CNS symptoms and brain/spinal MRI in patients with EGFR m+ NSCLC with LM and a clinically significant response rate in the brain in patients with EGFR m+ NSCLC with BM. The LM expansion cohorts for each drug may be further expanded to up to approximately 40 patients, respectively in order to confirm the safety and anti-tumour efficacy of AZD3759/AZD9291 in a larger group of patients. The BM expansion cohorts for each drug may be further expanded to up to approximately 30 patients, respectively in order to confirm the safety and anti-tumour efficacy of AZD3759/AZD9291 in a larger group of patients.

This study will also make preliminary assessment(s) of the effect of food on the exposure of AZD3759 and/or intra-patient varibility of the pharmacokinetics of a single dose.

Stopping criteria have been set in accordance with traditional oncology phase I study methodology.

5.3 Benefit/risk and ethical assessment

5.3.1 Potential benefits

In non-clinical animal models, AZD3759 has demonstrated profound anti-tumour efficacy in xenograft tumours implanted both subcutaneously and in the brain/leptomeninges. Based on these findings, AZD3759 may have the potential to provide clinical benefit to EGFR m+ advanced NSCLC patients, including induction of tumour regression, clearance of tumour cells in CSF (patients with LM), improvement of CNS symptoms and quality of life, and prolongation of survival. In addition, with the improved selectivity between wild type and mutant EGFRs, AZD3759 is expected to decrease wild type EGFR related toxicities caused by current EGFR TKIs.

In Part A of this study, AZD3759 has been shown to be well-tolerated, and preliminary anti-tumour activity has been observed both extracranially and intracranially in EGFR m+ advanced NSCLC patients who have relapsed after prior EGFR TKI therapy and chemotherapy. Based on the promising anti-tumour activity of AZD3759 even in the heavily pre-treated EGFR m+ NSCLC patients enrolled in Part A, Part B of the study will enrol EGFR TKI naïve patients in the BM expansion cohort. AZD3759 is anticipated to have optimal benefit in this patient population, in which acquired resistance to EGFR TKIs has yet to develop.

Recent non-clinical data showed that AZD9291 could also induce tumour regression in a EGFR m+ xenograft model implanted in the brain, suggesting its potential to cross blood brain barrier (BBB). In AURA study, there was anecdotal evidence of BM shrinkage in a number of patients (at doses 40–160 mg), and RECIST evidence of BM non-target lesion stabilisation (non-CR/non-PD) at all doses tested.

5.3.2 Potential risks

Non-clinical toxicity studies of AZD3759 in rats and dogs and safety pharmacology experiments and clinical safety finding from this study have been summarized in Section 2.2 of this protocol, which may indicate the potential risks of AZD3759 in human. Further detailed information of clinical and non-clinical toxicity findings is available in the IB. Clinical studies with AZD9291 are ongoing. Further details of both the clinical and non-clinical toxicity findings are available in the AZD9291 IB. The monitoring and management of the potential risks for both AZD3759 and AZD9291 is discussed below.

Gastrointestinal tract effects

Patients with refractory nausea and vomiting if not controlled by supportive therapy and chronic gastrointestinal diseases are excluded from participating in this study. Investigators will also be advised to follow the general toxicity management guidelines regarding dose interruption and reduction as detailed in Section 5.1.6 for both AZD3759 and AZD9291.

Dermatological effects

No specific dermatological exclusion criteria are included in this study, however, patients with any unresolved adverse event from prior therapy greater than CTCAE Grade 1 will be excluded from participation. Dermatological treatment should be instituted for patients with any CTCAE grade skin reactions, considered by the investigator to be causally related to AZD3759 or AZD9291. Investigators will also be advised to follow the general toxicity management guidelines regarding dose interruption and reduction as detailed in Section 5.1.6. Photographs may be performed to record any clinically significant findings. These photographs should be available for central review by AstraZeneca and AstraZeneca representatives if necessary.

Ocular surface effects

Full ophthalmic assessment, including slit lamp examination, will be performed in patients receiving either AZD3759 or AZD9291at screening and should be repeated if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated, as described in Section 5.1.6. 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 AZ and/or an AZ representative, if necessary. Ophthalmology examination results should be collected in the eCRF. Any patient developing corneal ulceration will be permanently discontinued from study treatment and should be followed regularly until resolution of the event. Patients who wear contact lenses will be advised to discontinue wearing lenses if they have any mild to moderate eye symptoms (CTCAE grade ≤2) while receiving treatment with AZD3759 or AZD9291 until at least one week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events they should discontinue wearing their contact lenses until at least one week after treatment with AZD3759 or AZD9291 is permanently discontinued and symptoms have resolved. Patients should 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 AZD3759 or AZD9291 has been permanently discontinued. Patients will be advised to consult the clinic promptly if they have any concerns.

Cardiovascular effects

Patients who have unstable cardiac conditions and risk factors for QT prolongations will be excluded from participation in this study. Concomitant use of regular medications that may prolong the QT interval will be restricted whenever feasible (See Appendix G, but patients may receive any medication that is clinically indicated for the treatment of AEs. Electrolyte and vital sign assessments, including pulse rate and blood pressure, will be monitored regularly throughout the study. A series of triplicate ECG assessments will be performed over a 24-hour period on the first day of dosing of AZD3759 in Part A andPart B, pre-dose on the first day of continuous dosing for both Part A and BM cohorts in Part B and over a 10 hour period at the time of presumed steady state (Day 8 of continuous dosing in Cycle 1) of both Part A and Part B and at the beginning of each subsequent treatment cycle. For AZD9291, a

series of triplicate digital ECG assessments will be performed over a 10-hour period on the first day of dosing, pre-dose of Day 8 and Day 15 of Cycle 1 and over 24-hour period on Day 1 of Cycle 2, and at the beginning of each subsequent treament cycle with AZD9291. The investigator or designated physician will review each ECG prior to discharge from the clinic and may refer to a local cardiologist if appropriate for immediate management of the patient. 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 AZD3759 cohorts, an Echocardiogram or MUGA scan to assess LVEF will be performed at screening prior to first dose of AZD3759 to evaluate any pre-existing cardiac abnormality and wherever and whenever necessary as clinically indicated throughout the study. For AZD9291 cohort, an Echocardiogram or MUGA scan to assess LVEF will be performed at screening (prior to first dose of AZD9291) and every 15 weeks throughout the treatment period.

Respiratory effects

Patients with a past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease will be excluded from participation in this study.

For patients receiving either AZD3759 or AZD9291, if new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca study team should be informed. A questionnaire regarding the results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters, bronchoscopy with biopsy as needed) will be sent to Investigators. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment 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.

Renal effects

Patients with abnormal renal function as defined by creatinine >1.5 x upper limit of normal (ULN) concurrent with creatinine clearance < 50 mL/min at screening are excluded from participating in the study. During the study, kidney function tests (creatine, urea nitrogen and Cystatin C) will be monitored regularly during the study and recorded at discontinuation.

Phototoxicity

Based on the potential for phototoxicity, patients receiving AZD3759 will be advised to wear protective clothing, sunglasses and use sun cream with UVA and UVB protection SPF≥30 when exposure to sunlight is anticipated and avoid use of sun tanning booths during the study and for 2 weeks after their last dose of AZD3759.

Liver effects

Patients with any evidence of severe or uncontrolled systemic liver disease, including those with known hepatitis B, hepatitis C, human immunodeficiency virus (HIV) or abnormal liver enzymes (defined as AST or ALT >2.5 x upper limit of normal (ULN), total bilirubin >1.5 x ULN if no evidence of liver metastases; AST or ALT >5 x ULN, total bilirubin >3 x ULN in the presence of liver metastases) at screening are excluded from participating in the study. For patients receiving either AZD3759 or AZD9291, liver function tests will be monitored regularly during the study and recorded at discontinuation. Patients' laboratory results will be assessed against the FDA's Draft Guidance for Drug Induced Liver Injury (FDA Guidance 2005), with the process described in detail in Appendix F.

Hematopoietic effects

Patients with inadequate bone marrow reserve 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) will be excluded from the study. For patients receiving either AZD3759 or AZD9291, haematological parameters will be monitored prior to administration of the first dose, weekly during the first cycle of multiple dosing, at the start of each subsequent cycle, and at discontinuation.

Reproductive organ effects

No reproductive toxicology or teratogenicity studies have been conducted with AZD3759 or AZD9291 to date, although the male and female reproductive tracts have been assessed as part of the 1 month toxicology studies. Therefore, women of child bearing potential and all men and their partners will be required to use adequate contraceptive measures during the study and for an appropriate period thereafter (as described in Section 5.1.2). Women of child bearing potential must have a negative pregnancy test prior to first dose of study treatment. Women who are breast feeding will be excluded from participating in the study. Male patients will be advised to arrange for the freezing of sperm samples prior to the start of the study should they wish to father children, and not to donate sperm until 3 months after discontinuation of study treatment.

Possible drug-drug interactions

All patients must try to avoid concomitant use of medications, herbal supplements and/or ingestions of foods with known potent inducer or inhibitory effects on CYP3A4/5 and/or CYP2C8 activity whenever feasible. Guidance on medications to avoid, medications that require close monitoring and on washout periods is given in Appendix G.

5.3.3 Overall benefit-risk and ethical assessment

For NSCLC patients with CNS metastases, the prognosis is very poor as there is no effective treatment available. This study is a first time in patient study with a BBB penetrable EGFR inhibitor, which potentially provides benefit to this population with high unmet medical need. A proportion of EGFR m+ NSCLC patients without CNS metastases might also benefit from the study due to the improved selectivity between wild type EGFR and mutant EGFR of

AZD3759 compared to current EGFR TKIs. The starting dose and steps for dose escalation of AZD3759 are selected based on non-clinical toxicity findings as well as applying well-established knowledge of wild type EGFR related toxicities. The selected starting dose is close to predicted human efficacious doses based upon data from non-clinical LM and BM models, in accordance with the ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Section III. A principle of selecting a dose 'that is expected to have pharmacologic effects'(ICH S9). In addition, patients will continue the treatment as long as they continue to derive benefit from the treatment according to ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals which states in Section III.C. that 'In Phase I clinical trials, treatment can continue according to the patient's response' (ICH S9).

Based on the non-clinical and clinical evidence from toxicity and anti-tumour efficacy studies of AZD3759, the study is designed to minimise potential risks and, maximize potential benefit to this group of patients who lack any effective treatment, as well as address the scientific hypothesis. In addition, applying the knowledge of known wild type EGFR related toxicities in clinic for the selection of starting dose and steps for dose escalation could lead to fewest possible cohorts exposed to AZD3759 below the presumed therapeutic dose.

Based on the recent non-clinical data indicating that AZD9291 has significant exposure in the brain and anti-tumour activity in EGFR m+ brain metastasis model, and the clinical data showing tumor response as well as good tolerability of AZD9291 at doses 40-160mg in EGFR m+ NSCLC patients with brain metastasis, 160mg of AZD9291 is also anticipated to bring benefit to patients with BM and/or LM with manageable risk of toxicities.

Therefore, the benefit/risk assessment for this phase I study appears to be acceptable.

5.4 Discontinuation of investigational product and withdrawal from study

There is no maximum duration of treatment for AZD3759/AZD9291 as patients may continue to receive study treatment beyond RECIST 1.1 progression as long as they are continuing to show clinical benefit, as judged by the investigator, agreed by AZ study physician, and in the absence of meeting any of the discontinuation criteria. Safety assessments should be continued as long as patients are receiving study treatment.

If study treatments are discontinued for reasons other than disease progression, the patient must continue RECIST 1.1 assessments and/or CSF cytology assessment (in case of patients with LM) every 6 weeks until disease progression, even if further lines of anticancer therapy are administered.

If study treatment continues after the patient experiences disease progression extracranially but with improved/stable intracranial disease, the patient should continue RECIST 1.1 assessments and/or CSF cytology assessment (in case of patients with LM) every 6 weeks until disease progression intracranially.

Patients experiencing corneal ulceration or Interstitial Lung Disease (ILD) will not be permitted to restart study treatment.

Patients may withdraw from any aspects of the voluntary exploratory research at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Section 6.7.5.

Patients may be discontinued from investigational product in the following situations:

- Patient decision. The patient is at any time free to withdraw his/her participation in the study, without prejudice
- Adverse events
- Severe non-compliance to this protocol as judged by the investigator and/or AstraZeneca
- Disease progression as per RECIST 1.1 and/or CSF cytology (in case of patients with LM) unless, in the opinion of the investigator, the patient is still receiving clinical benefit
- Patients incorrectly initiated on investigational product (Section 5.4.1)
- Pregnancy

Patients that are withdrawn from the study but who are evaluable per the definition in Section 5.1.4 for escalation cohorts or Section 7 for expansion cohorts will not be replaced. Any patient that is not evaluable will be replaced to ensure a minimum number of evaluable patients.

Once study medication is permanently discontinued it cannot be restarted.

A patient who discontinues study treatment is not always automatically withdrawn from the study. If a patient is withdrawn from study, see Section 5.4.2.

Any patient who discontinues study treatment for reasons other than disease progression should have tumour assessment (scans and/or CSF cytology) performed as scheduled in the protocol (see Table 4, Table 5 and Table 6) until disease progression is documented or death occurs, unless consent is withdrawn. Study procedure related SAEs and anti-cancer treatment must be captured until the patient no longer has tumour assessments (disease progression or permanent withdrawal from the study).

Data for AZD3759 will be collected until the primary DCO and AZD9291 data will be collected until final DCO, see Section 5.5.

Final database lock will occur following the final DCO for AZD9291. After the final database lock, there may be some patients remaining on study treatment. For these patients who are continuing to receive AZD3759/AZD9291 AZ will collect information during the treatment period and for 28 days (+ 7 days) after last dose on SAEs

5.4.1 Procedures for handling patients incorrectly initiated on investigational product

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

Where patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform the Sponsor Study Physician immediately. The decision on when to discontinue the ineligible patient from the study is based on the medical/safety risk for the patient. The Sponsor Study Physician is to ensure all such contacts are appropriately documented.

5.4.2 Procedures for withdrawal from study

Patients are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen by an investigator and undergo the assessments and procedures scheduled for the post study assessment (see Section 6.3.7). Adverse events should be followed up (see Sections 6.4.3 and 6.4.4) and the patient should return study drug.

5.5 Study timetable and end of study

Planned duration of the study:

The study started in September 2014.

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

There will be a primary data cut-off defined as the earlier of 7.5 months after the last patient starts investigational product or 28 days after the final patient discontinues investigational product. Data analysis will be performed and a Clinical Study Report written based on this data set.

Following the primary DCO, any AZD3759 patients still receiving investigational product at the time of the data cut-off will be able to continue to receive AZD3759 while deriving clinical benefit. Such patients will continue to be monitored for all Serious Adverse Events up to 28 days after the last dose of investigational product and reported to the sponsor using paper format. Drug Accountability information must still be collected until such patients have completed treatment.

Following the primary DCO, AZD9291 patients will continue to be followed up to a final data cut-off defined as 15 months after last patient starts dosing with AZD9291 or 50% OS maturity of AZD9291 T790M+ LM sub-cohort (whichever occurs latest.) The final data cut-off may happen earlier than 15 months if both median OS and median duration of response can be assessed earlier. The data analysis will be reported as an addendum to the Clinical Study Report (CSR).

Following the primary DCO, all assessment of AZD9291 patients will continue as before until final DCO except cognitive testing. Exploratory sample collection and testing may be removed without protocol amendment if the sponsor considers there is no need to continue. Safety ECGs will continue via local ECG.

Any AZD9291 patients still receiving investigational product at the time of the final data cut-off will be able to continue to receive AZD9291 while deriving clinical benefit. Such patients will continue to be monitored for all Serious Adverse Events up to 28 days after the last dose of investigational product and reported to the sponsor using paper format. Drug Accountability information must still be collected until such patients have completed treatment.

AZD3759 is not approved in any country. AZD9291(Tagrisso) is approved in some countries for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC). If applicable, for AZD9291 the IMP may be transitioned to commercial supply post final analysis at the same dose. Different drug supply options may be available depending on the country. Any changes to drug supply would be agreed with the patient and investigator.

6. STUDY PLAN AND COLLECTION OF STUDY VARIABLES

6.1 Study Plan

Assessments that are not mandatory for all patients are bracketed i.e. (X) in the Study Plan. Additional information regarding details of assessments can be located in the Sections as indicated in the far right column of the Study Plan. The schedule of assessments may change in response to emerging data, updated assessment tables will be provided outside of the protocol.

Descriptions of the procedures are included in the Table 4, Table 5 and Table 6. All study visits from Cycle 2 Day 1 onwards may be performed within a visit window of ± 2 days.

Table 4 Part A(SAD/MAD) Study Plan

	Screening	**Single dose/Cycle 0 (minimum of 3 day cycle)**			**Multiple Dose/Cycle 1 (21 day cycle)**			**Cycle 2 onwards (21 day cycle)**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Details in Section**
Visit (including Cycle 0)	1	1.1	1.2	1.3	2	3	4	5 onwards				
Visit (excluding Cycle 0)	1	Not Applicable			2	3	4	5 onwards				
Day	-28 to -1	D1	D2	D3	D1	D8	D15	D1				
Informed consent	x											Appendix C
Demography & baseline characteristics	x											6.3.1
Medical/surgical history	x											6.3.1
Inclusion/exclusion criteria	x											4
Physical / neurological examination	x	x			x			x	x			6.3.2
ECOG performance status	x	x			x			x	x			6.3.2
Ophthalmologic assessment	x								x			6.3.6.1
Hepatitis and HIV Screen	x											6.3.6.3
Vital signs	x	x	x		x	x		x	x			6.3.3
Height	x											6.3.3

Table 4 Part A(SAD/MAD) Study Plan

	Screening	Single dose/Cycle 0 (minimum of 3 day cycle)			Multiple Dose/Cycle 1 (21 day cycle)			Cycle 2 onwards (21 day cycle)	IP Discontinuation	28-day F/Up	Progression	Details in Section
Visit (including Cycle 0)	1	1.1	1.2	1.3	2	3	4	5 onwards				
Visit (excluding Cycle 0)	1	Not Applicable			2	3	4	5 onwards				
Day	-28 to -1	D1	D2	D3	D1	D8	D15	D1				
Weight	x	x			x			x	x			6.3.3
Clinical chemistry/ Haematology/Urinalysis	x	x			x	x	x	x	x			6.3.5
ECG	x	x	x		x	x		x	x			6.3.4
Pregnancy test (female of child-bearing potential only)	x	x							x			6.3.5
QLQ C-30	x				x			x (Every 6 weeks (relative to first dose of multiple dosing) until IP discontinuation)				6.9
QLQ BN-20	x				x			x	x			6.9
Blood for PK (Including metabolites)		x	x	x		x						6.5.1
Urine for PK (including metabolites)						x (0-12h)						6.5.1

Table 4 Part A(SAD/MAD) Study Plan

	Screening	**Single dose/Cycle 0 (minimum of 3 day cycle)**			**Multiple Dose/Cycle 1 (21 day cycle)**			**Cycle 2 onwards (21 day cycle)**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Details in Section**
Visit (including Cycle 0)	1	1.1	1.2	1.3	2	3	4	5 onwards				
Visit (excluding Cycle 0)	1	Not Applicable			2	3	4	5 onwards				
Day	-28 to -1	D1	D2	D3	D1	D8	D15	D1				
CSF for biomarkers (for patients without BM/LM at the time of enrolment but progressed with BM/LM during the study)											(x)	6.6.1.4
CSF for cytology, bio-chemistry, PK and biomarkers (LM patients only)	x					x (pre-dose)		x (Every 6 weeks (relative to first dose of multiple dosing) until progression)				6.5.1, 6.6.1.4, 6.8.1.2
CSF for PK and biomarkers (BM patients only)						x (pre-dose)		(x) (at progression or Cycle 5 Day 1, whichever occurs earlier)			(x) (at progression on Cycle5 Day 1,which occurs earlier)	6.5.1, 6.6.1.4
Blood-borne biomarker samples (plasma)	x					x		x (Every 6 weeks (relative to first dose of multiple dosing) until progression)				6.6.1.2

Table 4 Part A(SAD/MAD) Study Plan

	Screening	**Single dose/Cycle 0 (minimum of 3 day cycle)**			**Multiple Dose/Cycle 1 (21 day cycle)**			**Cycle 2 onwards (21 day cycle)**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Details in Section**
Visit (including Cycle 0)	1	1.1	1.2	1.3	2	3	4	5 onwards				
Visit (excluding Cycle 0)	1	Not Applicable			2	3	4	5 onwards				
Day	-28 to -1	D1	D2	D3	D1	D8	D15	D1				
Blood for PGx	(x)											6.6.2
Archival tumour tissue	x											6.6.1.1
Paired tumour biopsy	(x)					(x)						6.6.1.3
Echo/MUGA	x											6.3.6.2
CT/MRI imaging (modified RECIST)	x							x (Every 6 weeks (relative to first dose of multiple dosing) until progression)				6.8.1.1
Dose with AZD3759		x			< ----------Daily dosing ----------→							5.1
Concomitant Medication	< ---------- >											4.3.1
Adverse events	< ---------- >											6.4

Table 5 Part B Expansion Study Plan - LM

	Screening	**Multiple Dose/Cycle 1 (21 day cycle)**				**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit	1	2	2.1	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D8	D15	D1	D2	D1					
Informed consent	x												Appendix C
AZD9291 T790M+ sub-cohort only: submit sample for central confirmation of T790M+ mutation status	x												6.3.1
Demography & baseline characteristics	x												6.3.1
Medical/surgical history	x												6.3.1
Inclusion/exclusion criteria	x												4
Physical / neurological examination	x	x				x		x	x				6.3.2

Table 5 Part B Expansion Study Plan - LM

	Screening	Multiple Dose/Cycle 1 (21 day cycle)				Cycle 2		Cycle 3 onwards	IP Discontinuation	28-day F/Up	Progression	Survival follow-up	Details in Section
Visit	1	2	2.1	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D8	D15	D1	D2	D1					
ECOG performance status	x	x				x		x	x				6.3.2
Ophthalmologic assessment	x								x				6.3.6.1
Hepatitis and HIV Screen	x												6.3.6.3
Vital signs (AZD3759 cohorts)	x	x	x	x		x		x	x				6.3.3
Vital signs (AZD9291 cohorts)	x	x		x	x	x	x	x	x				6.3.3
Height	x												6.3.3
Weight	x	x				x		x	x				6.3.3
Clinical chemistry /Haematology/ Urinalysis	x	x		x	x	x		x	x				6.3.5

Table 5 Part B Expansion Study Plan - LM

	Screening	**Multiple Dose/Cycle 1 (21 day cycle)**				**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit	1	2	2.1	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D8	D15	D1	D2	D1					
ECG (AZD3759 cohorts)	x	x	x	x		x		x	x				6.3.4
ECG (AZD9291 cohorts)	x	x		x	x	x	x	x	x				6.3.4
Pregnancy test (female of child-bearing potential only)	x	x							x				6.3.5
QLQ C-30 and cognitive testing	x	x						x (Every 6 weeks (relative to first dose of multiple dosing) until IP discontinuation)					6.9
QLQ BN-20	x	x				x		x	x				6.9
Blood for PK (Including metabolites)—AZD3759 cohorts				x				x (C3D1 only)					6.5.1

Table 5 Part B Expansion Study Plan - LM

	Screening	**Multiple Dose/Cycle 1 (21 day cycle)**				**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit	1	2	2.1	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D8	D15	D1	D2	D1					
CSF for cytology, biochemistry, PK and biomarkers—AZD3759 cohorts	x			x (pre-dose)				x (Every 6 weeks (relative to first dose of multiple dosing) until progression)					6.5.1, 6.6.1.4, 6.8.1.2
Blood-borne biomarker samples (plasma)—AZD3759 cohorts	x			x				x (Every 6 weeks (relative to first dose of multiple dosing) until progression)					6.6.1.2
Blood for PK (Including metabolites)—AZD9291 cohorts		x		x	x	x	x						6.5.1

Table 5 Part B Expansion Study Plan - LM

	Screening	**Multiple Dose/Cycle 1 (21 day cycle)**				**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit	1	2	2.1	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D8	D15	D1	D2	D1					
CSF for cytology, biochemistry, PK and biomarkers—AZD9291 cohorts	x					x		x (every 6 weeks (relative to first dose of multiple dosing) until progression)					6.5.1, 6.6.1.4, 6.8.1.2
Blood-borne biomarker samples (plasma)—AZD9291 cohorts	x					x		x (every 6 weeks (relative to first dose of multiple dosing) until progression)					6.6.1.2
Blood for PGx	(x)												6.6.2
Archival tumour tissue	x												6.6.1.1
Paired tumour biopsy	(x)			(x)									6.6.1.3
Echo/MUGA (AZD3759 cohorts)	x												6.3.6.2

Table 5 Part B Expansion Study Plan - LM

	Screening	**Multiple Dose/Cycle 1 (21 day cycle)**				**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit	1	2	2.1	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D8	D15	D1	D2	D1					
Echo/MUGA (AZD9291 cohorts)	x	<----------15 weekly relative to first dose---------- >											6.3.6.2
CT/MRI imaging (modified RECIST)	x							x (Every 6 weeks (relative to first dose of multiple dosing) until progression)					6.8.1.1
Dose with AZD3759/AZD 9291		< ----------Daily dosing ---------- >											5.1
Concomitant Medication	< ---------- ---- >												4.3.1
Adverse events	< ---------- ---- >												6.4
Survival follow-up												x (Every 6 weeks)	6.3.7

Table 6 Part B Expansion Study Plan – BM (including assessment of food effect and intra-patient variability)

	Screen-ing	**Assessment of Food Effect / intra-patient variability / Cycle 0**				**Multiple Dose / Cycle 1 (21 day cycle)**			**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit (AZD3759 cohorts)	1	1.1	1.2	1.4	1.5	2	3	4	5	5.1	6 onwards					
Visit (AZD9291 cohorts)	1	Not Applicable				2	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D4	D5	D1	D8	D15	D1	D2	D1					
Informed consent	x															Appendix C
Demography & baseline characteristics	x															6.3.1
Medical/surgical history	x															6.3.1
Inclusion/exclusion criteria	x															4
Physical/ neurological examination	x	x				x			x		x	x				6.3.2
ECOG performance status	x	x				x			x		x	x				6.3.2
Ophthalmologic assessment	x											x				6.3.6.1

Table 6 Part B Expansion Study Plan – BM (including assessment of food effect and intra-patient variability)

	Screen-ing	**Assessment of Food Effect / intra-patient variability / Cycle 0**				**Multiple Dose / Cycle 1 (21 day cycle)**			**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit (AZD3759 cohorts)	1	1.1	1.2	1.4	1.5	2	3	4	5	5.1	6 onwards					
Visit (AZD9291 cohorts)	1	Not Applicable				2	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D4	D5	D1	D8	D15	D1	D2	D1					
Hepatitis and HIV Screen	x															6.3.6.3
Vital signs (AZD3759 cohorts)	x	x	x			x	x		x		x	x				6.3.3
Vital signs (AZD9291 cohorts)	x					x	x	x	x	x	x	x				6.3.3
Height	x															6.3.3
Weight	x	x				x			x		x	x				6.3.3
Clinical chemistry/ Haematology/Urinalysis	x	x				x	x	x	x		x	x				6.3.5
ECG (AZD3759 cohorts)	x	x	x			x	x		x		x	x				6.3.4

Table 6 Part B Expansion Study Plan – BM (including assessment of food effect and intra-patient variability)

	Screen-ing	**Assessment of Food Effect / intra-patient variability / Cycle 0**				**Multiple Dose / Cycle 1 (21 day cycle)**			**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit (AZD3759 cohorts)	1	1.1	1.2	1.4	1.5	2	3	4	5	5.1	6 onwards					
Visit (AZD9291 cohorts)	1	Not Applicable				2	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D4	D5	D1	D8	D15	D1	D2	D1					
ECG (AZD9291 cohorts)	x					x	x	x	x	x	x	x				6.3.4
Pregnancy test (female of child-bearing potential only)	x	x										x				6.3.5
QLQ C-30 and cognitive testing	x					x					x (Every 6 weeks (relative to first dose of multiple dosing) until IP discontinuation)					6.9
QLQ BN-20	x					x			x		x	x				6.9
Blood for PK (Including metabolites)—AZD3759 cohorts		x	x	x	x		x				x (C3D1 only)					6.5.1

Table 6 Part B Expansion Study Plan – BM (including assessment of food effect and intra-patient variability)

	Screen-ing	**Assessment of Food Effect / intra-patient variability / Cycle 0**				**Multiple Dose / Cycle 1 (21 day cycle)**			**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit (AZD3759 cohorts)	1	1.1	1.2	1.4	1.5	2	3	4	5	5.1	6 onwards					
Visit (AZD9291 cohorts)	1	Not Applicable				2	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D4	D5	D1	D8	D15	D1	D2	D1					
Blood for 4β hydroxycholesterol (induction marker)—AZD3759 cohorts		x (pre-dose)						x								6.5.1
CSF for PK and biomarkers—AZD3759 cohorts							x (pre-dose)				(x) (at progression or Cycle 5 Day 1 whichever occurs earlier)			(x) (at progression or Cycle 5 Day 1 whichever occurs earlier)		6.5.1, 6.6.1.4

Table 6 Part B Expansion Study Plan – BM (including assessment of food effect and intra-patient variability)

	Screen-ing	**Assessment of Food Effect / intra-patient variability / Cycle 0**				**Multiple Dose / Cycle 1 (21 day cycle)**			**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit (AZD3759 cohorts)	1	1.1	1.2	1.4	1.5	2	3	4	5	5.1	6 onwards					
Visit (AZD9291 cohorts)	1	Not Applicable				2	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D4	D5	D1	D8	D15	D1	D2	D1					
Blood-borne biomarker samples (plasma) — AZD3759 cohorts	x						x				x (Every 6 weeks (relative to first dose of multiple dosing) until progression)					6.6.1.2
Blood for PK (Including metabolites)— AZD9291 cohorts						x	x	x	x	x						6.5.1

Table 6 Part B Expansion Study Plan – BM (including assessment of food effect and intra-patient variability)

	Screen-ing	**Assessment of Food Effect / intra-patient variability / Cycle 0**				**Multiple Dose / Cycle 1 (21 day cycle)**			**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit (AZD3759 cohorts)	1	1.1	1.2	1.4	1.5	2	3	4	5	5.1	6 onwards					
Visit (AZD9291 cohorts)	1	Not Applicable				2	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D4	D5	D1	D8	D15	D1	D2	D1					
CSF for PK and biomarkers—AZD9291 cohorts									x (pre-dose)		(x) (at progression or Cycle 5 Day 1 whichever occurs earlier)			(x) (at progression or Cycle 5 Day 1 whichever occurs earlier)		6.5.1, 6.6.1.4
Blood-borne biomarker samples (plasma) — AZD9291 cohorts	x								x		x (every 6 weeks (relative to first dose of multiple dosing) until progression)					6.6.1.2
Blood for PGx	(x)															6.6.2

Table 6 Part B Expansion Study Plan – BM (including assessment of food effect and intra-patient variability)

	Screen-ing	**Assessment of Food Effect / intra-patient variability / Cycle 0**				**Multiple Dose / Cycle 1 (21 day cycle)**			**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit (AZD3759 cohorts)	1	1.1	1.2	1.4	1.5	2	3	4	5	5.1	6 onwards					
Visit (AZD9291 cohorts)	1	Not Applicable				2	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D4	D5	D1	D8	D15	D1	D2	D1					
Archival tumour tissue	x															6.6.1.1
Paired tumour biopsy	(x)						(x)									6.6.1.3
Echo/MUGA (AZD3759 cohorts)	x															6.3.6.2
Echo/MUGA (AZD9291 cohorts)	x					<------15 weekly relative to first dose------ >										6.3.6.2
CT/MRI imaging (modified RECIST)	x										x (Every 6 weeks (relative to first dose of multiple dosing) until progression)					6.8.1.1
Dose with AZD3759/AZD9291		x		x		< ----------Daily dosing ---------- >										5.1

Table 6 Part B Expansion Study Plan – BM (including assessment of food effect and intra-patient variability)

	Screen-ing	**Assessment of Food Effect / intra-patient variability / Cycle 0**				**Multiple Dose / Cycle 1 (21 day cycle)**			**Cycle 2**		**Cycle 3 onwards**	**IP Discontinuation**	**28-day F/Up**	**Progression**	**Survival follow-up**	**Details in Section**
Visit (AZD3759 cohorts)	1	1.1	1.2	1.4	1.5	2	3	4	5	5.1	6 onwards					
Visit (AZD9291 cohorts)	1	Not Applicable				2	3	4	5	5.1	6 onwards					
Day	-28 to -1	D1	D2	D4	D5	D1	D8	D15	D1	D2	D1					
Concomitant Medication	< ---------- - >															4.3.1
Adverse events	< ---------- - >															6.4
Survival follow-up															x (Every 6 weeks)	6.3.7

6.2 Recording of data

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

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

For details of data and study management see Appendix D of this Clinical Study Protocol.

6.3 Safety procedures

Prior to discharge from each in-patient and clinic visit, the Investigator or their deputy will be responsible for reviewing all available safety data, including vital signs and ECGs.

6.3.1 Enrolment and screening

At enrolment, each potential patient will provide informed consent prior to starting any study specific procedures (see Appendix C of this Clinical Study Protocol for Ethics and Regulatory Requirements).

Each potential patient is assigned a unique enrolment number. If a patient withdraws from the study, then the enrolment code cannot be reused.

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

A standard medical, medication and surgical history will be obtained with review of the selection criteria with the patient.

For patients in AZD9291 T790M+ LM sub-cohort, it is recommended the screening assessments be performed in a stepwise process beginning with the confirmation of T790M status as determined by the designated central laboratory. However, screening assessments may be done in parallel to the T790M mutation assessment, as appropriate. Before blood based T790M testing is set up at the designated central laboratory, only recent tumour biopsy will be collected for T790M status confirmation and should be taken following progression on the latest line of therapy. After blood based T790M testing is set up at the designated central laboratory, tumour biopsy (preferred if available) and/or blood sample will be collected from each patient at screening and the confirmation of T790M status will be based on either tumour or blood. Any residual material from this biopsy and/or blood may be used for exploratory analysis.

Each patient will undergo screening (see Study Plan Table 4, Table 5 and Table 6) up to 28 days prior to first dosing (see Sections 4.1 and 4.2). 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 the first dose of study treatment.

6.3.2 Physical examination

A physical examination will be performed and include 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 (see Table 4, Table 5 and Table 6). A separate "neurological examination" CRF will need to be completed in addition to the general "Physical examination" CRF.

Performance status will be assessed at the visits as indicated in the Study Plan (see Table 4, Table 5 and Table 6) according to ECOG 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 eg, 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

6.3.3 Vital signs

Supine blood pressure and pulse rate

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 4, Table 5 and Table 6). Observations will be recorded at the following times:

AZD3759 cohorts:

- Screening
- First dosing day (Day 1 Cycle 0 for Part A and Day 1 Cycle 0 for BM expansion of Part B): pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dose
- First day of multiple dosing (Day 1 Cycle 1 for LM expansion of Part B): pre-dose, 1, 2, 4, 6 and 10 and 24 hours post-dose
- First day of multiple dosing (Day 1 Cycle 1 for Part A and Day 1 Cycle 1 for BM expansion of Part B): pre-dose

- Presumed steady state (Day 8 Cycle 1): pre-dose, 1, 2, 4, 6 and 10 hours postdose
- On Day 1 of each subsequent Cycle: one assessment at any time during day
- On occurrence of any cardiac AE
- Discontinuation visit

AZD9291 cohorts:

- Screening
- First dosing day (Day 1 Cycle 1): pre-dose, 1, 2, 4, 6 and 10 hours post-dose
- Day 8 and Day 15, Cycle 1: pre-dose only
- Day 1, Cycle 2: pre-dose, 1, 2, 4, 6, 10 and 24 hours (Day 2) post-dose
- On Day 1 of each subsequent Cycle; one assessment at any time during day
- On occurrence of any cardiac AE
- Discontinuation visit

A 15 min window will be allowed for vital signs assessment performed at pre-dose and1-10 h; and a 1 h window for vital signs assessment performed at 24 h. The timing and frequency of vital signs assessment may be adjusted in response to emerging PK and safety profile.

Weight

Weight will be performed at screening and then Day 1 of each cycle and at the discontinuation visit.

Height

Height will be assessed at screening only.

Any changes in vital signs should be recorded as an AE if applicable.

6.3.4 ECG

Resting 12-lead ECG

A 12-lead ECG will be performed at the visits as shown in the Study Plan (see Table 4, Table 5 and Table 6) at the following times:

AZD3759 cohorts:

- Screening

- First dosing day (Day 1 Cycle 0 for Part A and Day 1 Cycle 0 for BM expansion of Part B): pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dose
- First day of multiple dosing (Day 1 Cycle 1 for LM expansion of Part B): pre-dose, 1, 2, 4, 6, 10 and 24 hours post-dose
- First day of multiple dosing (Day 1 Cycle 1 for Part A and Day 1 Cycle 1 for BM expansion of Part B): pre-dose
- Presumed steady state (Day 8 Cycle 1): pre-dose, 1, 2, 4, 6 and 10 hours postdose
- On Day 1 of each subsequent Cycle: one assessment at any time during day
- On occurrence of any cardiac AE
- Discontinuation visit

AZD9291 cohorts:

- Screening
- First dosing day (Day 1 Cycle 1): pre-dose, 1, 2, 4, 6 and 10 hours post-dose
- Day 8 and Day 15, Cycle 1: pre-dose only
- Day 1, Cycle 2: pre-dose, 1, 2, 4, 6, 10 and 24 hours (Day 2) post-dose
- On Day 1 of each subsequent Cycle; one assessment at any time during day
- On occurrence of any cardiac AE
- Discontinuation visit

The timing and number of ECGs may be adjusted in response to the emerging PK and safety profile.

A 15 min window will be allowed for ECGs performed at pre-dose and1-10 h; and a 1 h window for ECG performed at 24 h.

Twelve-lead ECGs will be obtained after the patient has been resting supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. For each time point three ECG recordings should be taken at about 2 minute intervals. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study, where feasible. Where possible for existing patients, and for new patients enrolled onto the study, ECGs will be recorded on machines that store the records in a digital file.

For AZD3759 patients, 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. Digital ECG (dECG) records where they exist will also be retained for each patient and transferred for central analysis, as required (e.g. Heart rate, PR, R-R, QRS and QT intervals may be determined and reviewed by an external cardiologist). If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent medical history condition. If there is a clinically significant abnormal ECG findings during the treatment period, this should be recorded on the AE CRF, according to standard adverse events collection and reporting processes (see Section 6.4.3). For all ECGs details of rhythm, PR, R-R, QRS and QT intervals and an overall evaluation will be recorded. All ECGs of patients with any value of >470ms QTcF are to be sent for immediate review to the study team.

ECG data (with the exception of the screening ECGs) of the AZD9291 cohort will be collected digitally and 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. After the primary DCO, ECGs of AZD9291 LM patients will be performed via local ECG until final DCO and will not be transferred for central analysis.

If sufficient digital ECG data exists from the AZD3759 patients on this study, a prospectively planned concentration-QTcF analysis will be performed with the purpose of assessing the effect of the drug on the QTc interval with a high degree of confidence, as described in the ICH E14 document for QT/QTc assessment, using digital ECG and plasma AZD3759 concentrations collected during part A (single and multiple ascending dose phase) and part B (dose expansion phase) of this study. The data will be first assessed for hysteresis and then for linearity, to decide if a linear model or a non-linear model should be used, prior to analysis.

6.3.5 Laboratory safety assessment

Blood and urine samples for safety assessments will be taken at the following visits:

- Screening
- First dosing day (Day 1 Cycle 0 for Part A and BM expansion of Part B, Day 1 Cycle 1 for LM expansion of Part B): pre-dose
- First day of multiple dosing (Day 1 Cycle 1 for Part A and BM expansion of Part B): pre-dose
- Weekly during Cycle 1 (Day 8, Day 15): pre-dose
- On Day 1 of each subsequent Cycle: pre-dose
- Discontinuation visit

All the laboratory safety assessments will be conducted at local labs. Laboratory tests do not need to be repeated at baseline if the baseline visit is within 7 days of the screening sample.

The timing of blood samples may be altered depending on the emerging PK and safety profile. Additional sampling times may be added if indicated by the emerging data.

Laboratory values that meet the criteria for CTCAE grade 3 or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.

The following laboratory variables will be measured:

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- Leukocyte differential count:
S/P-Calcium, total	Neutrophils
S/P-Creatinine	Lymphocytes
S/P-Glucose	Monocytes
S/P-Magnesium	Basophils
S/P-Potassium	Eosinophils
S/P-Sodium	B-Platelet count
S/P-Urea nitrogen	B-Reticulocytes
S/P-Cystatin C	Urinalysis
	U-Glucose
	U-Protein
	U-Blood

Additionally a urine/serum sample will be collected from all females of child-bearing potential at screening, before first dose, and at treatment discontinuation for a pregnancy test.

Cases where a subject shows an AST or ALT ≥3xULN or total bilirubin ≥2xULN may need to be reported as SAEs. Prompt reporting of cases meeting Hy's law criteria (via the SAE expedited reporting system) is required for compliance with regulatory guidelines. The investigator is responsible for, without delay, determining whether a patient meets potential Hy's law criteria.

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

For blood volume see Section 6.7.1.

6.3.6 Other safety assessments

6.3.6.1 Ophthalmologic examination

Full ophthalmologic assessment, including slit lamp examination, should be performed at screening, study drug discontinuation and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings. These photographs should be available for central review by AZ and AZ representatives if necessary. Ophthalmology examination results should be collected in the eCRF.

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

6.3.6.2 Echocardiogram/MUGA Scan

For AZD3759 cohorts, an Echocardiogram or MUGA scan to assess LVEF will be conducted at screening (prior to first dose of AZD3759) and whenever necessary as clinically indicated throughout the study. For AZD9291 cohorts, an Echocardiogram or MUGA scan to assess LVEF will be performed at screening (prior to first dose of AZD9291) and every 15 weeks throughout the treatment period. The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans if required. The patients should also be examined using the same machine and operator where possible.

6.3.6.3 Hepatitis screen, HIV screen

All patients will be screened for Hepatitis B surface antigen (HBsAg). Screening for Hepatitis C will be based on HCV antibodies.

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot.

Appropriate counselling will be made available by the Investigator in the event of a positive finding. Notification of regional and/or national authorities, if required by law, will be the responsibility of the Investigator.

Results will be available as source data and will not be recorded within the CRF.

6.3.7 Follow-up

A post study assessment will be performed at the time investigational product is permanently discontinued (see Study Plan Table 4, Table 5 and Table 6).

As a minimum, telephone contact should be made with the patient 28 days following the discontinuation of AZD3759/AZD9291 to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy). Refer to Section 6.4.3 for full details on AE recordings during follow-up.

Once the 28-day follow-up visit is complete, all patients in expansion cohorts will be followed for overall survival, via telephone contact, every 6 weeks until the patient dies or lost to follow-up or withdraws consent. Any additional therapies given for NSCLC should be captured at these times, via the eCRF.

6.4 Adverse events

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

6.4.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition during or following exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, 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.

Any deterioration of the disease under study and associated symptoms or findings should not be regarded as an adverse event as far as the deterioration can be anticipated.

The term adverse event is used generally to include any AE whether serious or non-serious.

6.4.2 Definitions of serious adverse events

A serious adverse event (SAE) 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 or results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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

For definition of other significant adverse events (OAE) see Section 7.3.1.

6.4.3 Recording of adverse events

Time period for collection of adverse events

AEs will be collected throughout the study, from informed consent until the end of the follow-up period. The follow-up period is defined as 28 days (+7 days) after study treatment is discontinued. SAEs occurring in the follow-up period should be reported to AstraZeneca in the usual manner (see Section 6.4.4).

Following discontinuation of AZD3759/AZD9291, SAEs considered related to study procedures should continue to be collected as outlined in Table 7.

After the final database lock, there may be some patients remaining on study treatment. For these patients who are continuing to receive AZD3759/AZD9291, AstraZeneca will collect information (during the treatment period and for 28 days after last dose) on SAEs, deaths (including those due to disease progression), discontinuation due to AEs/SAEs

Table 7 Summary of recording and follow-up of adverse events

	Consent to Treatment Period	Until 28-day Follow-up Visit (safety follow-up period)	Post 28-day Follow-up visit but prior to progression (if applicable)
Collect all new AEs in CRF	Yes	Yes	No
Collect all ongoing AEs in CRF	Yes	Yes	Yes
Collect all study procedure-related SAEs in CRF	Yes	Yes	Yes

Follow-up of unresolved adverse events

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

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 related to AZD3759/AZD9291, the investigator should notify AstraZeneca.

Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date when the AE started and stopped
- CTCAE grade
- 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

For SAEs other variables will be collected including treatment given for the event.

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 6.4.2. 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. 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.

The grading scales found in the current National Cancer Institute CTCAE version will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the current CTCAE version can be downloaded from the Cancer Therapy Evaluation Programme website (http://ctep.cancer.gov).

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 procedure. 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 of this Clinical Study Protocol.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: *‘Have you 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.

Adverse events based on examinations and tests

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarised in the Clinical Study Report. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the criteria for a SAE, a DLT or are the reason for discontinuation of treatment with the investigational product unless clearly due to progression of disease under study (see Disease progression).

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 (eg, anaemia versus low haemoglobin value). In the absence of clinical signs and symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

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.

Disease progression

Disease progression can be considered as a worsening of a patient'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. **Events that are unequivocally due to disease progression should not be reported as AEs during the study.**

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 patient's inclusion in this study. They do not include metastases of the original cancer.

Hy's Law

Cases where a subject shows an AST or ALT ≥3xULN or total bilirubin ≥2xULN may need to be reported as SAEs. Prompt reporting of cases meeting Hy's law criteria (via the SAE expedited reporting system) is required for compliance with regulatory guidelines. The

investigator is responsible for, without delay, determining whether a patient meets potential Hy's law criteria.

Details of identification of potential Hy's law cases and actions to take are detailed in Appendix F.

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

6.4.4 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.

If any SAE occurs in the course of the study, then investigators 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 the necessary information is provided to the appropriate AstraZeneca patient safety data entry site within **one calendar day** of initial receipt for fatal and life threatening events and within **five 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 immediately, or **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 Section 6.3.7 of the Investigators Brochure for AZD3759/AZD9291.

6.5 Pharmacokinetics

6.5.1 Collection of pharmacokinetic samples

Part A

Venous blood samples (approximately 4 mL) for determination of concentrations of AZD3759 and characterisation of its metabolites in plasma will be taken at the times presented in Table 8. The date and time of collection of each sample will be recorded. Plasma samples will be split into two aliquots (~ 1mL each), one for quantification of AZD3759 and the N-demethylated metabolite and another for identification and semi-quantification of all possible metabolites.

Urine samples (approximately 5 mL) for the determination of concentrations of AZD3759 and characterisation of its metabolites will be taken from the total urine sample provided during 0-12h at Cycle 1 Day 8 (Table 4). The date and time of collection and the weight of each urine collection will be recorded. Samples will be split into two aliquots, one (~1 mL) for quantification of AZD3759 and the N-demethylated metabolite and another (~4mL) for identification and semi-quantification of all possible metabolites.

Part B

Venous blood samples (approximately 2 mL) for quantification of AZD3759 and the N-demethylated metabolite in plasma will be taken at the times presented in Table 9 and Table 10. Venous blood samples for determination of concentrations of AZD9291 and its metabolites (AZ5104 and AZ7550) in plasma will be taken at the times presented in Table 11. The date and time of collection of each sample will be recorded.

For BM expansion, venous blood samples (approximately 5 mL) to evaluate if AZD3759 affects 4b-hydroxy cholesterol in plasma will be taken at pre-dose of Cycle 0 Day 1 and Cycle 1 Day 15 (Table 6). The two samples should be taken at the same time of the day.

CSF collection

For patients with BM, one CSF sample (approximately 0.3mL) for PK analysis will be collected at pre-dose of Cycle 1 Day 8 (AZD3759 cohorts) or pre-dose of Cycle 2 Day 1

(AZD9291 cohorts) only. If for any reason the CSF sample could not be obtained from the patients, the investigator should inform and discuss with AZ Study Delivery Team Leader.

For patients with LM, two CSF samples (approximately 0.3mL) for PK analysis will be collected at pre-dose of Cycle 1 Day 8 (AZD3759 cohorts) or pre-dose of Cycle 2 Day 1 (AZD9291 cohorts), and Cycle 3 Day 1 (coincide with CSF sampling for cytology assessment), respectively.

Table 8 PK blood sample schedule (Part A)

Time relative to dose	**Single Dosing (Cycle 0)**			**Multiple Dosing (Cycle 1)**
	Day 1	Day 2	Day 3	Day 8
Pre-dose	X			X
0.5 hours	X			X
1 hour	X			X
1.5 hours	X			X
2 hours	X			X
3 hours	X			X
4 hours	X			X
6 hours	X			X
8 hours	X			X
10 hours	X			X
12 hours	X			X
24 hours		X		
48 hours			X	

Table 9 PK blood sample schedule (LM Expansion-AZD3759 treatment)

Time relative to dose	**Multiple Dosing (Cycle 1) Day 8**	**Multiple Dosing (Cycle 3) Day 1**
Pre-dose	X	X
0.5 hours	X	X
1 hour	X	X
1.5 hours	X	X
2 hours	X	X
3 hours	X	X
4 hours	X	X

Table 9 PK blood sample schedule (LM Expansion-AZD3759 treatment)

Time relative to dose	Multiple Dosing (Cycle 1) Day 8	Multiple Dosing (Cycle 3) Day 1
6 hours	X	X
8 hours	X	X
10 hours	X	X
12 hours	X	X

Table 10 PK blood sample schedule (BM Expansion-including food effect/intra patient variability assessment- AZD3759 treatment)

Time relative to dose	Single Dosing (Cycle 0) – fed or fasted				Multiple Dosing (Cycle 1)	Multiple Dosing (Cycle 3)
	Day 1	Day 2	Day 4	Day 5	Day 8	Day 1
Pre-dose	X		X		X	X
0.5 hours	X		X		X	X
1 hour	X		X		X	X
1.5 hours	X		X		X	X
2 hours	X		X		X	X
3 hours	X		X		X	X
4 hours	X		X		X	X
6 hours	X		X		X	X
8 hours	X		X		X	X
10 hours	X		X		X	X
12 hours	X		X		X	X
24 hours		X		X		

Table 11 PK blood sample schedule (LM/BM Expansion-AZD9291 treatment)

Time relative to Dose	Multiple Dosing (Cycle 1)			Multiple Dosing (Cycle 2)
	Day 1	Day 8	Day 15	Day 1
Pre-dose	X	X	X	X
1 hour				X

Table 11 PK blood sample schedule (LM/BM Expansion-AZD9291 treatment)

Time relative to Dose	Multiple Dosing (Cycle 1)			Multiple Dosing (Cycle 2)
	Day 1	Day 8	Day 15	Day 1
1.5 hours				X
2 hours				X
4 hours				X
6 hours				X
8 hours				X
10 hours				X
12 hours				X
24 hours				X (D2, pre-dose)

A 5 min window will be allowed for samples taken at 0.5 h and 1 h; a 10 min window for samples taken at 1.5-10 h; a 15 min window for samples taken at pre-dose; a 1 h window for samples taken at 12 h and 24 h; and a 2 h window for samples taken at 48 h.

The timing of the pharmacokinetic samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration-time profiles. The total volume of blood taken from each patient until end of Cycle 1will not exceed that detailed in Section 6.7.1. Any residual sample remaining after PK analysis has been performed may be used for exploratory biomarker research and characterisation of metabolites, if consent for this exploratory research has been obtained. In order to monitor potential drug-drug interactions while the patients are taking some concomitant medications, additional blood and/or CSF samples may be collected and assayed for AZD3759 and the N-demethylated metabolite, e.g. pre-dose and 1.5h post-dose of the day by when the drug concentrations are presumed to reach steady state. The decision to take additional PK samples will reside with the SRC.

If a patient misses any doses of AZD3759/AZD9291 within 3 days of PK sampling, please contact the AstraZeneca Study Delivery Team Leader as to any effect on the changes required on the timing of the PK assessments. All other assessments, including laboratory safety assessments, vital signs and RECIST should continue to be performed as per study plan, relative to baseline assessments.

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

6.5.2 Determination of drug concentration in pharmacokinetic samples

Samples for determination of AZD3759 and N-demethylated metabolite in plasma, urine and CSF and AZD9291 and its metabolites AZ5104 and AZ7550 in plasma and CSF will be 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 (i.e., AZD3759 and its metabolites; and AZD9291 and its metabolites) at the time of receipt by the bioanalytical laboratory will be analysed.

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

6.6 Exploratory research

6.6.1 Exploratory biomarker research

If a patient agrees to participate in the exploratory biomarker research component of the study biological samples will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug 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 study drug to generate hypotheses to be tested in future studies.

6.6.1.1 Collection of archival tumour samples

All patients 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 patient treatment must be clearly indicated for each sample provided. Tumour samples will preferably be 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, 10-20 slides of freshly prepared unstained 5 micron sections from the archival tumour block may be provided. As uncontrolled oxidation processes affect tumour sections, tumour tissue blocks are preferred. The archival tumour samples will be sent to a central lab for retrospective confirmation of EGFR mutation status with a well-validated EGFR mutation test. From submitted archival tumour blocks, material may be taken for exploratory biomarker analysis (including 2 cores in order to construct tissue micro arrays) or for later biomarker analysis. The remaining part of the tumour block can be returned to the institution.

Collection for archival tumour samples is mandatory for all patients if available. Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

6.6.1.2 Collection of exploratory blood-borne biomarkers

Approximately 20 mL blood sample will be collected to provide plasma to evaluate genetic mutations including but not limited to EGFR mutations that may be predictive of the activity of AZD3759/AZD9291. For sampling schedule, see Study Plan (Table 4, Table 5 and Table 6).

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

6.6.1.3 Collection of paired biopsy tumour samples

To evaluate the effect of AZD3759/AZD9291 on inhibiting pEGFR signals and the genetic mutations in extracranial tumours, paired tumour biopsy will be collected. Formalin fixed paraffin embedded (FFPE) biopsies at screening and Cycle 1 Day 8 will be obtained for patients with accessible extracranial lesions where patients' consent has been obtained. If for any reason the biopsy cannot be collected at Cycle 1 Day 8 it may be taken at any visit until end of Cycle 1. On-treatment biopsy timing may be refined with emerging pharmacokinetic data during the course of the trial. Accessible lesions are defined as tumour lesions, which are biopsiable, and amenable to repeat biopsy, unless clinically contraindicated or the patient has withdrawn consent. Failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will not be considered a protocol deviation.

Paired tumour biopsy is optional for all patients. Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

6.6.1.4 Collection of exploratory CSF biomarkers

Approximately 4 mL CSF sample will be collected from patients with LM for cytology slides preparation for POM and POP study at screening and Cycle 1 Day 8 (AZD3759 cohorts) or Cycle 2 Day 1 (AZD9291 cohorts) to assess modulation of pEGFR in tumour cell pellet with AZD3759/AZD9291 treatment. If for certain reasons some patients may not participate in CSF POM and/or POP study, the agreement should be reached between site and AstraZeneca before the patient receives the first dosing.

Approximately 0.7 mL (minimum 0.5mL) CSF sample will be collected from patients with LM at screening, Cycle 1 Day 8 (AZD3759 cohorts) or Cycle 2 Day 1 (AZD9291 cohorts), and every 6 weeks (relative to first dose of multiple dosing) until disease progression to evaluate genetic mutations including but not limited to EGFR mutations, that may be predictive of the activity of AZD3759/AZD9291.

Approximately 0.7 mL (minimum 0.5ml) CSF sample will be collected from patients with BM at Cycle 1 Day 8 (AZD3759 cohorts) or Cycle 2 Day 1 (AZD9291 cohorts), and Cycle 5 Day 1 or disease progression (whichever occurs earlier) to evaluate genetic mutations including but not limited to EGFR mutations, that may be predictive of the activity of AZD3759/AZD9291. The 2nd CSF sample is not mandatory.

For patients without BM/LM at the time of enrolment, but progressed with BM/LM during the study, an optional CSF (approximately 0.7 mL, minimum 0.5mL) sample will be collected at disease progression to evaluate genetic mutations as well. Once sufficient exploratory CSF have been collected to draw scientific conclusions, this sample collection may be stopped by the sponsor without protocol amendment.

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

6.6.2 Pharmacogenetics

If a patient agrees to participate in the host pharmacogenetics research component of the study a blood sample will be collected. The results of this pharmacogenetic research will be reported separately and will not form part of the Clinical Study Report.

6.6.2.1 Collection of pharmacogenetic samples

The 9 mL blood sample for pharmacogenetic research will be obtained from the patients immediately prior to administration of the first dose of AZD3759/AZD9291. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event. Such patients would be important to include in any pharmacogenetic analysis. If for any reason the sample is not drawn prior to dosing it may be taken at any visit until the last study visit. Only one sample should be collected per patient for pharmacogenetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

6.6.3 LANO assessment score change

An additional independent assessment of LM imaging will be performed via BICR for the AZD9291 LM cohort. The assessment will be conducted by one single qualified neuro-radiologist assigned to perform independent reads of study brain and/or spine MRI and/or CT scans, using a single-read model.

At baseline, the neuro-radiologist will make an assessment of the CNS lesions and will classify the baseline scan as showing presence or absence of LM. Each follow-up scan will then be assessed for LM disease only. A total score of all LM lesions will be recorded at each post-baseline time point using LANO criteria (Chamberlain M et al 2017) (Table 12). The LM BICR read will follow the guidelines detailed in an addendum to the BICR Charter.

Assessment of brain and/or spine imaging will be performed qualitatively, as a whole, and compared to baseline with no measurements being performed. No modifications will be made to the previously completed brain metastases review data during the LM review. The reviewer will record a LANO assessment score for each time point as follows (Table 12):

- At baseline, the reviewer assesses presence of LM in terms of: 1, 0 and non-evaluable (NE) due to image quality issues.

- At post-baseline time points, the reviewer assesses LM in terms of: +3, +2, +1, 0, -1, -2, -3, NE.
- If the LANO assessment score was NE, the reviewer records pertinent comments.

Table 12 LANO assessment score definitions

	Assessment LANO score	LM BICR assessment (RECIST-like)
Baseline		
LM present	1	
LM absent	0	
Not evaluable	NE	
Post-baseline		
Completely resolved	+3	CR
Definitely improved	+2	PR
Possibly improved	+1	SD
Unchanged	0	SD
Possibly worse	−1	SD
Definitely worse	−2	PD
New site of disease	−3	PD
Not evaluable	NE	

NE = not evaluable due to image quality issue(s)/missing anatomy.

If directed by the Sponsor at a later date, an additional independent assessment of LM imaging will be performed via BICR for the AZD3759 LM cohort.

6.7 Biological sampling procedures

6.7.1 Volume of blood and CSF

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on AZD3759/AZD9291 become available. The estimated total volume of blood that will be drawn from each patient until end of Cycle 1 in this study for mandatory and optional samples is 200 mL.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

Up to approximately 8 mL CSF will be drawn from patients with LM at screening, Cycle 1 Day 8 (AZD3759 cohort) or Cycle 2 Day 1(AZD9291 cohort), and every 6 weeks (relative to first dose of multiple dosing) until disease progression. CSF samples will be prioritized for cytology assessment and POM biomarker analysis. Approximately 1 mL CSF will be drawn from patients with BM at Cycle 1 Day 8 (AZD3759 cohort) or Cycle 2 Day 1(AZD9291 cohort) for PK analysis and evaluation of genetic mutations.

Additional blood/CSF samples may be taken for further exploratory analysis if consent has been obtained from the patient.

6.7.2 Handling, storage and destruction of biological samples

The samples will be used up, or disposed of after analyses or retained for further use as described below.

Any pharmacokinetic sample remaining after analysis for AZD3759 and its metabolites may be used for biomarker analyses. These analyses are for AstraZeneca use only and will not be included in the Clinical Study Report.

Biological samples for future research will be retained at AstraZeneca or its designee, on behalf of AstraZeneca for a maximum of 15 years following the last patient's last visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in a Clinical Study Report Addendum /Scientific Report or Scientific Publication.

6.7.2.1 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. Anonymised samples will be retained for no more than 5 years after the CSR is finalised.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report.

Samples for metabolite identification and/or analysis will be shipped to and retained by Innovation Center China (ICC), AstraZeneca for a maximum of one year following the finalisation of the Clinical Study Report. The results from the investigation will not be reported in the Clinical Study Report but in a separate report.

6.7.2.2 Samples for exploratory research

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

Each sample for exploratory research will be identified with the study number and patient enrolment number. In this way exploratory biomarker and genetic data may be correlated with clinical data, samples destroyed in the case of withdrawal of consent and regulatory audit enabled.

Where genetic analysis will be undertaken the processes adopted for the coding and storage of samples will be more stringent in order to maintain patient confidentiality. As an added precaution, irrespective of the type of 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 will be used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff) working with the DNA.

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping and Translational Science 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 when the patient has requested disposal/destruction of collected samples not yet analysed.

6.7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B of this Clinical Study Protocol ‘IATA 6.2 Guidance Document’.

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

6.7.4 Chain of custody of biological samples

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

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

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

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

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

6.7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of voluntarily donated biological samples, then 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.

If collection of the biological samples is an integral part of the study, then the patient may be withdrawn from further participation in the study.

The Principal Investigator:

- Ensures AstraZeneca is notified immediately of the patient's withdrawal of informed consent to the use of donated biological samples
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal

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

6.8 Anti-tumour activity

6.8.1 Tumour assessments

6.8.1.1 Imaging assessment

RECIST 1.1 criteria will be used to assess patient response to treatment by determining Objective Response rate (ORR), Disease Control Rate (DCR), Duration of Response (DOR) and Progression Free Survival (PFS). The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) will be modified for the separate assessment of extracranial disease and CNS disease (brain metastases (BM) and leptomeningeal disease) according to Appendix E.

Imaging assessments will be performed using CT/MRI scan of the chest and abdomen (including liver and adrenal glands) at baseline within 28days of treatments start and then every 6 weeks ± 1week (relative to first dose of multiple dosing) until objective disease progression or withdrawal from study. In addition, all patients will have a brain MRI scan at

baseline and at follow-up in patients with confirmed brain metastases and/or leptomeningeal disease on the baseline brain scan. Spinal MRI should be performed in patients with suspected or known leptomeningeal disease involving the spinal column at baseline and follow-up. In addition, additional areas should be investigated based on the signs and symptoms of the patient. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

Categorisation of objective tumour response assessment for extracranial disease will be based on the RECIST 1.1 criteria of response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

CNS disease (brain metastases and leptomeningeal disease) will be assessed separately from extracranial disease using RECIST 1.1 criteria and a separate assessment of CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

In addition the investigator will be asked to record an assessment for leptomeningeal disease of complete response, responding, stable or progressing in addition to assessment as part of the non target lesions for CNS response assessment.

Progression will be recorded as the visit response if there is progression extracranial disease and or CNS disease. An overall visit response will be derived by combining the CNS and extracranial disease time point responses (Appendix E).

For objective response rate (ORR), a visit response of CR or PR must be confirmed by a later scan conducted at the next scheduled visit and no less than four weeks after the initial visit response of CR or PR.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTL (non-target lesion) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If 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 level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan (Table 4, Table 5 and Table 6) and Appendix E, Section 5.1.

Central reading of scans

A collection of all scans used in the assessment of tumours using modified RECIST 1.1 may be conducted so that these are available should a central review be required. All imaging assessments including unscheduled visit scans may be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organisation (CRO) for central analysis. Currently an independent review is planned of brain and spinal scans in patients with leptomeningeal disease. Additional reviews may be performed. For AZD9291 LM patients (and potentially AZD3759 LM patients), an independent assessment of LM imaging using LANO criteria (Chamberlain M et al 2017) will be performed. The assessment will be conducted by one single qualified neuro-radiologist assigned to perform independent reads of study brain and/or spine MRI and/or CT scans, using a single-read model, please refer to section 6.6.3. Results of planned or unplanned independent reviews will not be communicated to Investigators, and the management of patients will be based solely upon the results of the RECIST assessment conducted by the Investigator.

6.8.1.2 CSF cytology assessment and CSF biochemistry

CSF cytology test is one of the key measurements to evaluate the anti-tumour effect of AZD3759/AZD9291 in patients with LM. CSF biochemistry test could serve as a supportive evidence to demonstrate the anti-tumour effect of AZD3759/AZD9291 in patients with LM.

Approximately 3 ml of CSF will be collected from patients with LM at screening, Cycle 1 Day 8 (AZD3759 cohorts) or Cycle 2 Day 1(AZD9291 cohorts), and every 6 weeks ± 1 week (relative to first dose of multiple dosing) until disease progression. The CSF sample will be split into two aliquots, one (approx . 2mL) of which will be sent to local cytopathology lab to assess the presence of tumour cells, another (approx . 1mL) will be sent to local bio-chemistry lab to determine the content of glucose and protein in CSF. A patient is a CSF responder at a visit if they have 100% clearance of tumour cells from CSF. Otherwise they are a CSF non-responder. CSF responses must be confirmed by a later CSF collection conducted at the next scheduled visit and no less than four weeks after the initial CSF response.

6.8.1.3 Neurological Examination

Neurological exam is another key measurement to evaluate the anti-tumour effect of AZD3759/AZD9291 in patients with LM. Neurological examination will be performed at the same schedule as the general physical examination.

6.8.2 Correlative studies, special studies and functional imaging

Not applicable.

6.9 Patient Reported Outcomes

Patient reported outcome (PRO) is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. 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 BN-20 and CogState cognitive testing.

6.9.1 QLQ C-30 and QLQ BN-20

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993. It consists of 30 items and measures cancer patients' functioning (Health Related Qulaity of Life) and symptoms (Aaronson N et al 1993). The EORTC QLQ-BN20 was developed for use among brain cancer patients varying in disease stage and treatment modality (i.e. surgery, chemotherapy, radiotherapy, etc.). It should always be complemented by the QLQ-C30 (Taphoorn M et al 2010). Relevant symptom questions from QLQ-BN20 will be used to explore CNS symptom improvement.

6.9.2 Administration of PROs

Questionnaires will be administered using paper questionnaires. The patient should complete the questionnaires at the scheduled clinic visit at baseline, and throughout the study at the times specified in the study plan (Table 4, Table 5 and Table 6). If any scheduled PRO assessment is not completed the reason for non-completion should be recorded.

PROs will be filled out prior to any other site activities and encounters with physician. The patients will be instructed to complete the PRO independently. This site will have a designated quiet space for patients to use when completing the assessments. Each centre should allocate responsibility for PRO assessment to a specified individual (e.g. a research nurse).

It is important that the value and relevance of Health Related Qulaity of Life (HRQoL) data are explained carefully to participating patients so that they are motivated to comply with data collection. The research nurse or appointed individual should also stress that the information is confidential.

Therefore, if the patient has any medical problems she should discuss them with the doctor or research nurse separately from their HRQoL assessment.

The instructions for completion of questionnaires are:

- It must be completed before any investigations or discussions about the status of the patient's disease with the clinic staff.
- The patient must complete it themselves without any intervention from family, friends, centre staff etc.
- The only exception to this is if the patient is blind or illiterate. In this case the questionnaire may be read to the patient verbatim, however the reader must not aid in the interpretation of questions or in the selection of answers.

- Only one answer to every question should be checked.
- Centre personnel should not review the responses to the questionnaire with the patient or with any other centre staff.

Following completion, the nurse or appointed individual may quickly scan the questionnaire visually for completeness and should confirm verbally with the patient that the questionnaire has been completed fully.

6.9.3 Cognitive test

Clinical trials of treatments for brain tumours (either primary or brain metastases) or other cancers commonly include the measurement of cognition (also referred to as neurocognition). The FDA has indicated that "improvement in neurocognitive function or delay in neurocognitive progression are acceptable end points" (Meyers C et al 2006). Specifically, neurocognitive outcomes can be used where the treatment has risk of neurotoxicity or to provide evidence of clinical benefit. Neurocognition has been shown to be associated with diminished independence in activities of daily living, can impact quality of life, can predict prognosis, and may decline in advance of imaging evidence of progression. In cases where treatment does not improve overall survival or progression free survival, improvements or maintenance of functional independence/quality of life would arguably be of substantial value. The most commonly noted cognitive impairments are seen in the domains of learning and memory, processing speed and executive function (Wefel J et al 2011).

If possible, all patients in Part B will participate in the following computerized cognitive tests provided by Cogstate.

One Card Learning Task (OCL; Visual Recognition Memory)

The One Card Learning task is a measure of visual recognition memory and uses a well-validated pattern separation paradigm using playing card stimuli. In this task, the playing cards are identical to those found in a deck of playing cards with the exception of the joker. The subject is asked whether the card currently being presented in the center of the screen was seen previously in this task. The subject responds by pressing the Yes or No key. Because no card has been presented yet, the first response is always No. The software measures the speed and accuracy of each response.

Detection Task (DET; Processing Speed)

The Detection task is a measure of information processing speed and uses a well-validated simple reaction time paradigm using playing card stimuli. In this task, the stimuli are all the same joker card. The subject is asked to press the Yes key as soon as the card in the center of the screen turns face up. The software measures the speed and accuracy of each response.

Identification Task (IDN; Attention/Vigilance)

The Identification task is a measure of visual attention and uses a well-validated choice reaction time paradigm using playing card stimuli. In this task, the playing cards are all either

red or black jokers. The subject is asked whether the card currently being presented in the center of the screen is red. The subject responds by pressing the Yes key when the joker card is red and No when it is black. The software measures the speed and accuracy of each response.

One Back Memory Task (OBK; Working Memory)

The One Back Memory task is a measure of working memory and uses a well-validated n-back paradigm using playing card stimuli. In this task, the playing cards are identical to those found in a deck of playing cards with the exception of the joker. The subject is asked whether the card currently being presented is the same as the one presented immediately previously. The subject responds by pressing the Yes or No key. Because no card has been presented yet, the first response is always No. The software measures the speed and accuracy of each response.

7. EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS

7.1 Definition of study endpoints

To meet the objectives for this study, data for the following endpoints will be collected:

- Safety and Tolerability (Primary)
- AZD3759 pharmacokinetics in plasma, urine and CSF (Secondary and Exploratory)
- AZD9291 pharmacokinetics in plasma and CSF (Secondary)
- 4b-hydroxy cholesterol in AZD3759 Part B patients with BM (Secondary)
- Tumour response (Secondary) including:
  - Objective response rate (ORR), disease control rate, duration of response, and change from baseline in tumour size by modified RECIST for CNS disease and for extracranial disease;
  - ORR, disease control rate, duration of response for overall;
  - Response rate, disease control rate and duration of response by Investigator's assessment of leptomeningeal disease;
  - PFS for Part B patients
  - CSF response rate for patients with LM
  - Neurological function improvement rate for patients with LM

  - Overall survival for Part B patients

- Patient Reported Outcomes (Secondary and Exploratory)
- Metabolite identification/pharmacokinetics (Exploratory)
- Biomarkers (Exploratory)
- Pharmacogenetics (Exploratory)
- CSF biochemistry (Exploratory)

Safety endpoints are defined in Sections 6.3 and 6.4. Derivations, calculations and analysis plans for each of these endpoints are presented in Section 7.3.

7.2 Determination of sample size

The primary objective of this study is to investigate the safety and tolerability and thereby identify the MTD of AZD3759 (if possible) and to recommend dose(s) for evaluation in future clinical studies. Hence the number of patients has been based on the desire to obtain adequate tolerability, safety and pharmacokinetic and pharmacodynamic data while exposing as few patients as possible to the investigational product and procedures.

Part A

For the dose escalation phase of the study, cohorts of 3-6 evaluable patients will be required. The total number of patients will depend upon the number of dose escalations necessary. It is anticipated that there will be approximately 5 escalation cohorts, hence up to approximately 30 evaluable patients will be required.

Part B

For the dose expansion phase of the study, cohorts of approximately 12 patients with LM and approximately 15 patients with BM will be accrued and treated at the recommended dose of AZD3759 for further clinical evaluation to explore further the tolerability, pharmacokinetics and biological activity at this/these dose(s). Similar cohorts will be accrued for treatment with AZD9291 at 160 mg once daily.

The rationale for the BM cohort size is based on a target value (TV) rate of 60% which is the approximate observed response rate for EGFR TKI treatment naïve BM patients, and a 50% response rate as a lower reference value (LRV) which is a level at which clinical significance would be minimal. If a response is seen in 10 or more of the 15 patients, then there is at least an 80% probability that the true ORR is equal or greater than the LRV. If an objective response is seen in 6 or fewer patients then there is less than a 10% probability that the true rate of ORR is greater than the TV.

For LM, clinical efficacy is less robustly defined and the TV and LRV have been set as: TV= 30%, LRV=10%. If a CSF response is seen in 3 or more of the 12 patients, then there is at

least an 80% probability that the true response rate is equal or greater than the LRV. If an objective response is seen in 1 or fewer patients then there is less than a 10% probability of the true rate of ORR is greater than the TV.

If, after assessing 12-15 patients in an LM or BM expansion cohorts, the response rate is such that further investigation of AZD3759, AZD9291 or both is required, then one or more cohorts may be further expanded. Each BM cohort will be expanded up to approximately 30 and LM cohort up to approximately 40 patients primarily to gain more evidence on safety but also to allow a better estimate of ORR and an early estimate of overall survival. There will be an 80% chance of seeing at least one incidence in 40 patients of a safety signal that occurs in 4% of patients in the target population. Based on 20 efficacy responses out of 40, the 2-sided 80% confidence interval for the true ORR would be (39%, 61%).

The total number of patients will depend upon the number of dose expansions necessary. It is anticipated that there will be up to approximately 3 LM expansion cohorts (up to 2 for AZD3759 and 1 for AZD9291) with up to approximately 40 subjects per cohort, and up to approximately 3 BM expansion cohorts with up to approximately 30 subjects per cohort may be used, hence up to approximately 210 evaluable patients will be required.

7.3 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, ECG changes. These will be collected for all patients. Appropriate summaries of these data will be presented.

ECG Changes

Immediate clinical management of patients will be according to local assessment of the QT interval. For the Clinical Study Report QTc will be calculated using Fridericia's formula.

$QTcF = QT/ (3\sqrt{RR})$

Creatinine Clearance

Estimated creatinine clearance will be calculated using the Cockcroft and Gault formula as below:

For creatinine values in mol/L

Men: [(140 – age) x weight (kg) x 1.23] / creatinine (µmol/L)

Women: [(140 – age) x weight (kg) x 1.04] / creatinine (µmol/L)

7.3.1 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of investigational product. Based on the expert's judgement, adverse events of particular clinical

importance may, after consultation with the Global Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the Clinical Study Report. A similar review of laboratory values, vital signs, ECGs and other safety assessments will be performed for identification of other significant adverse events.

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

7.4 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the plasma and urine concentration data for AZD3759 and N-demethylated metabolite and plasma AZD9291and metabolites AZ5104 and AZ7550 will be performed by QCP, Alderley Park, AstraZeneca or its delegate The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods.

Where possible the following PK parameters will be determined for AZD3759 and AZD9291 and their metabolites.

Following the single dose part (or first dose) of the study, the following parameters, if applicable, will be determined

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal rate constant (λ_z), terminal half life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to 24 hours ($AUC_{(0-24)}$), from zero to 12 hours ($AUC_{(0-12)}$),from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and from zero to infinity (AUC), apparent plasma clearance (CL/F), apparent volume of distribution (V_{ss}/F;), mean residence time (MRT)

Following the multiple dose part of the study, the following parameters, if applicable, will be determined.

Maximum plasma concentration at steady state ($C_{ss\ max}$), time to $C_{ss\ max}$ ($t_{ss\ max}$), minimum plasma concentration at steady state ($C_{ss\ min}$), area under the plasma concentration-time curve from zero to the end of the dosing interval (AUC_{ss}), apparent plasma clearance at steady state (CL_{ss}/F), extent of accumulation on multiple dosing (R_{AC}), time dependency of the pharmacokinetics. For AZD3759 only, renal clearance (CLR) and amount of drug excreted unchanged (Ae; % dose).

The maximum plasma concentration (C_{max}), the C_{max} at steady state ($C_{ss\ max}$), the time of maximum concentration (t_{max}) and the t_{max} at steady state ($t_{ss\ max}$) will be determined by inspection of the concentration-time profiles. Where possible the terminal elimination rate constant (λ_z) will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data and the terminal half-life ($t_{½\lambda z}$) will be calculated as $\ln 2/\lambda_z$. The area under the concentration-time curve up to the last quantifiable sample ($AUC_{(0-t)}$) and the area under the concentration-time curve up to 24 hours ($AUC_{(0-24)}$)

and up to 12 hours ($AUC_{(0-12)}$) will be calculated using the linear up, log down trapezoidal rule. Where appropriate, the $AUC_{(0-t)}$ will be extrapolated to infinity using λ_z to obtain AUC. The area under the concentration-time curve across the dosing interval, AUC_{ss} will be calculated using the linear up, log down trapezoidal rule. The apparent clearance (CL/F following the single dose and CL_{ss}/F following multiple dosing) will be determined from the ratio of dose/AUC or dose/AUC_{ss}. The volume of distribution (V_{ss}/F) will be determined from the mean residence time (MRT) x CL/F and the accumulation ratio (R_{AC}) for AZD3759 will be calculated as the ratio of the $AUC_{(0-12)}$ on cycle 1, Day 8to cycle 0, Day 1 in part A or cycle 0 day1/4 fasted from part B . The time dependency of the pharmacokinetics on multiple dosing for AZD3759 will be assessed by the calculation of the ratio of $AUC_{(0-12)}$ cycle 1 Day 8/AUC cycle 0 Day 1 or cycle 0 day1/4 fasted.

Where possible the appropriate pharmacokinetic parameters will also be determined for N-demethylated metabolite of AZD3759 and the metabolites AZ5104 and AZ7550 of AZD9291.

7.5 Calculation or derivation of exploratory research variables

Potential relationship between relevant efficacy measures, biomarkers or safety variables and plasma or CSF concentration of AZD3759 (or N-demethylated metabolite) and AZD9291 (or its metabolites) maybe explored and models maybe developed to describe relevant relationship. These data may also be pooled with other data. Only the results from the following exploratory endpoints will form part of the Clinical Study Report (CSR): PROs**,** CSF biochemistry and intra-patient variability of the plasma PK of a single dose of AZD3759.

A prospectively planned concentration-QTcF analysis will be performed using the available digital ECG data and concentrations with the purpose to assess the effect of the drug on the QTc interval with a high degree of confidence. The same criteria to assess “negative QTc results” (The upper bound of the 2-sided 90% confidence interval (CI) of the predicted placebo-adjusted ΔQTcF is below 10 ms at clinically relevant plasma levels of the drug”), as described in the ICH E14 for QT/QTc assessment, using high quality digital ECG and concentrations collected during Part A (single and multiple ascending dose) and part B (expansion) of the Phase 1 study. The data will be first assessed for hysteresis and then for linearity, to decide if a linear model or a non-linear model should be used.

LANO assessments will be mapped to RECIST-like scores as shown in Table 12. Best LM BICR assessment will be derived for patients with LM present at baseline, without a requirement for confirmation.

7.6 Calculation or derivation of tumour response variables

The main tumour analysis will use local assessments. Centrally reviewed scans may also be reported.

At each visit all patients will be programmatically assigned a modified RECIST extracranial visit response depending on the status of their disease compared with baseline and previous visit assessments. In addition, patients with CNS disease will be programmatically assigned a CNS RECIST visit response as described in section 6.8.1.

Overall visit response will be derived as from the extracranial time-point response and CNS time-point response (Appendix E). Overall visit response for patients diagnosed with both extracranial and CNS disease will also be derived in the same way.

In addition, investigator assessment of complete response, responding, stable disease and progressive disease will be collected for patients with leptomeningeal disease (Section 6.8.1.1).

Overall tumour response will be reported for all patients. In addition CNS and extracranial response will be reported separately and for patients diagnosed with both diseases for BM and LM patients and Investigator assessment of leptomeningeal disease reported for patients with leptomeningeal disease.

For RECIST, progression of TLs 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.

If a patient has had a tumour assessment, which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) unless there is evidence of progression in which case the response will be assigned as PD.

For TL measurements, if ≤ 1/3 of the TL sizes are missing then a scaling up rule will be applied as follows:

- If ≤ 1/3 of lesions recorded at baseline are missing then the results will be scaled up (based on the baseline sizes) to give an estimated sum of diameters and this will be used in calculations (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the baseline sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing)

- If > 1/3 of lesions recorded at baseline are missing then the TL response will be NE. However, if the sum of non-missing TL diameters would result in PD (ie, if using a value of 0 for missing lesions the sum of diameters has still increased by > 20% or more compared to the smallest sum of diameters on study), PD takes precedence over NE

A visit response of CR will not be allowed if any of the TL data is missing

The following tumour response variables will then be derived:

Modified RECIST for overall tumour response– all patients

- Best objective response/objective response rate
- Duration of response

- Disease control rate
- Progression free survival by modified RECIST (Part B)

Modified RECIST for CNS disease – BM /LM patients

- CNS best objective response/objective response rate
- Duration of CNS response
- CNS disease control rate
- For measurable CNS BM patients, week 6 and week 12 percentage change in tumour size

Modified RECIST for EXC disease – BM /LM patients

- CNS best objective response/objective response rate
- Duration of CNS response
- CNS disease control rate
- For measurable CNS BM patients, week 6 and week 12 percentage change in tumour size

Modified RECIST for both CNS and EXC disease – BM and LM patients

- CNS and EXC best objective response/objective response rate
- Duration of CNS and EXC response
- CNS and EXC disease control rate

In addition for patients with LM

- Best response/ response rate
- LM disease control rate
- Duration of LM response

7.6.1 Objective response and best response rate (Modified RECIST)

Objective response rate is defined as the percentage of patients who have at least one confirmed response of CR or PR prior to any evidence of progression (as defined by RECIST 1.1 or modified RECIST). Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR.

A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions. A confirmed response of CR/PR means that a response of CR/PR is recorded

at one visit and confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.

For patients with leptomeningeal disease, response rate is defined as the percentage of patients who have at least one confirmed response of Complete Response or Responding prior to any evidence of progression (as defined by modified RECIST). Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of best response rate.

7.6.2 Disease control rate

Disease control rate is defined as the proportion of patients with a best overall, extracranial, CNS, and both extracranial and CNS response of confirmed CR, confirmed PR, or SD.

For patients with leptomeningeal disease, disease control rate is defined as the proportion of patients with a best response of confirmed CR, confirmed responding, or stable disease.

In the case of stable disease, assessments should have met the stable disease criteria for at least 6 weeks after the study start.

7.6.3 Duration of Response (Modified RECIST)

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 (responding for leptomeningeal disease assessment) 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.

7.6.4 Change in tumour size (Modified RECIST)

Tumour size is defined as the sum of the lengths of the longest diameters of the RECIST 1.1 target lesions. Percentage change in tumour size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs compared to baseline. The best change in tumour size (defined as the maximum reduction from baseline or the minimum increase from baseline, in the absence of a reduction) will include all assessments prior to progression or start of subsequent anti-cancer therapy. Missing target lesion data at visits may be imputed using appropriate imputation rules.

Change in tumour size will be reported separately for extracranial disease and CNS only. Overall change in tumour size will not be calculated.

For further details see Appendix E of this Clinical Study Protocol.

7.6.5 Progression Free Survival

PFS is defined as the time from date of first dosing until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdraws from AZD3759/AZD9291 therapy or receives another anti-cancer therapy prior to progression.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two visits of baseline.

If a patient discontinues treatment prior to progression and/or receives a subsequent therapy prior to progression then these patients will continue to be followed until evidence of objective disease progression and their PFS time will be derived as defined above.

The PFS time will always be derived based on scan/assessment dates and not visit dates.

Modified RECIST assessment times 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 progression
- When censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment

Note: Symptomatic deterioration will not be regarded as a progression event.

7.6.6 CSF response rate

CSF response rate is defined as the percentage of LM patients who have at least one CSF response (100% clearance of tumour cells from CSF) prior to any evidence of progression. CSF responses must be confirmed by a later CSF collection conducted at the next scheduled visit and no less than four weeks after the initial CSF response.

7.6.7 Overall survival

Overall survival, assessed at the end of the study for BM and LM patients in Part B, will be derived as the time **from** date of first dose of AZD3759 or AZD9291 to the date of death (from any cause). Subjects who are alive or lost to follow-up at the end of the study will be censored at the last recorded date that the subject is known to be alive or at the date of data cut-off (whatever occurs earlier).

7.7 Description of analysis sets

The analysis of data will be based on different subsets according to the purpose of the analysis. Throughout the safety results sections, erroneously treated patients (eg, those

assigned to receive dose A who actually received dose B, those who failed to meet the selection criteria) will be accounted for in the actual dose group received.

Analysis sets are presented in Table 13.

Table 13 Analysis sets

Analysis Set	Definition
All patients	All patients screened
Safety	All patients who received at least 1 dose of AZD3759/AZD9291.
Safety (BM patients only)	Subset of safety set: BM patients in Part B.
Pharmacokinetics	All dosed patients with at least one reportable[a] AZD3759/AZD9291 plasma concentrations and no important adverse events or protocol deviations that may impact PK
PK (BM patients only)	Subset of PK set: BM patients in Part B.
Food effect (BM patients only)	Patients from the food effect cohort for whom a PK profile is available on at least one of the fed and fasted dosing days
Evaluable for response (Part B)	Dosed patients in Part B with disease at baseline
Evaluable for CNS response	Dosed patients with measurable CNS disease at baseline
Evaluable for extracranial disease response	Dosed patients with extracranial disease at baseline
Evaluable for CSF response (LM))	Dosed patients with tumour cells in CSF at baseline
CSF biochemistry	Dosed patients with at least one evaluable CSF biochemistry result
Evaluable for LM response	Dosed patients with LM disease at baseline
Exploratory biomarkers	All patients that participate in the exploratory biomarker research

[a] "reportable" includes all patients, even those with drug levels BLQ.

7.8 Methods of statistical analysis

The statistical analyses will be performed by designated third party provider, under the direction of the Biostatistics Group, AstraZeneca.

Data from the dose escalation phase (Part A) and the dose expansion phase (Part B) will be presented separately. Data from the AZD3759 cohort and the AZD9291 cohort will be presented separately and reported in separate CSRs.

In the escalation phase, safety, PK and baseline data will be summarised by dose phase and efficacy data will be summarised by metastasis type and dose. In the expansion phase, data will be summarised by metastasis type and dose. In addition AZD3795 data will be summarised by EGFR TKI status in Part B. AZD9291 data will also be summarised by T790M cohort, in the interim analysis only LM patients will be summarized.

The AZD3759 data from this study will be summarised and will include a paired comparison of the effect of food, a repeated measures analysis of CSF biochemistry and a mixed effects model comparing intra-patients variability of plasma PK. No further formal statistical analysis will be carried out.

Demographic data

Demographic data will be summarised using the safety analysis set.

Characteristics of the patients, including medical history and disease characteristics at baseline will be listed for each patient and summarised. Previous brain radiotherapy will be used to stratify best objective response as assessed by Independent Central Review (ICR), as well as being listed.

Reasons for discontinuation of investigational product will be listed including the study day of treatment discontinuation and will be summarised.

Exposure

Exposure data will be summarised using the safety analysis set.

Exposure to investigational product ie, total amount of study drug received will be listed for all patients.

Total exposure (date of last dose minus date of first dose +1) and actual exposure (excluding dose interruptions) will be summarised by the following: mean, standard deviation, minimum, maximum, median and total treatment years. In addition, the number and percentage of patients with at least one dose interruption/dose delay, at least one dose reduction, and at least one modification will be presented separately for Part A and Part B. Relative dose intensity (RDI; the percentage of the actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation) and percentage intended dose (PID; the percentage of the actual dose delivered relative to the intended dose through progression) will also be summarised separately for Part A and B.

Safety

Safety data will be summarised using the safety analysis set.

Safety data will not be formally analysed. At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

Data from all cycles in Part A will be combined in the presentation of safety data, and likewise for Part B. AEs will also be listed individually by patient and dose group. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group. The number of patients experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade. The number and percentage of patients with adverse events in different categories (eg, causally related, CTCAE grade ≥3 etc) will be summarised by dose group, and events in each category will be further summarised by MedDRA system organ class and preferred term, by dose group. SAEs, dose limiting toxicities and other significant AEs (as defined by the Global Safety Physician) will be summarised separately if a sufficient number occur.

Any AE occurring before the first dose of investigational product (ie, before study Day 1) will be included in the data listings reported in a separate summary tables of adverse events.

Any AE occurring within the defined 28 day follow-up period after discontinuation of investigational product will be included in the AE summaries. Any adverse events in this period that occur after a patient has received further therapy for cancer (following discontinuation of investigational product) will be flagged in the data listings. AEs occurring after the 28 day follow-up period after discontinuation of investigational product will be listed separately, but not included in the summaries.

Haematology, clinical chemistry, vital signs, ECG data, ophthalmic examination data, Echo/MUGA demographic data, medical histories and concomitant medications will be listed individually by patient and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used.

Details of any deaths will be listed for all patients.

Any qualitative assessments will be summarised for all patients using the number of patients with results of negative, trace or positive.

Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline.

Pharmacokinetics

This will be summarised using the Pharmacokinetics analysis set.

Plasma concentrations of AZD3759/AZD9291 and metabolites will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by dose level. Parameters following single and multiple dosing will be summarised separately. Plasma concentrations at each time point will be summarised according to dose by the following summary statistics:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- Gmean ± standard deviation (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Median
- Minimum
- Maximum
- Number of observations

The following summary statistics, as applicable, will be presented for AUC, $AUC_{(0-12)}$, $AUC_{(0-24)}$, $AUC_{(0-t)}$, AUC_{ss}, C_{max}, $C_{ss\ max}$ and $C_{ss\ min}$:

- Gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- CV, calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Median
- Minimum
- Maximum
- Number of observations

The following summary statistics, as appropriate, will be presented for CL/F, CL_{ss}/F, volume of distribution, $t_{½\lambda z}$, R_{AC}, two point calculation (TPC):

- Arithmetic mean
- Standard deviation
- Median
- Minimum
- Maximum
- Number of observation

The following summary statistics will be presented for t_{max} and $t_{max\ ss}$:

- Median
- Minimum
- Maximum
- Number of observations

If applicable, the pharmacokinetic data for AZD3759/AZD9291 and metabolites after a single-dose and separately, after multiple doses will also be displayed graphically. Displays will include plasma concentration patient profiles (on the linear and log-scale) versus time and gmean concentration (+/-standard deviation) versus time, stratified by dose.

If applicable, scatter plots of PK parameters versus dose, or log-dose will also be considered following both single and multiple dose administration of AZD3759/AZD9291 to assess dose proportionality.

Tumour response

The analysis set for best objective response, objective response rate and disease control rate will be the evaluable for response analysis set for modified RECIST, evaluable for LM response analysis set for Investigator assessments, the evaluable for CNS response analysis set for brain RECIST, the evaluable for extracranial response set for extracranial RECIST, and the evaluable for CNS and extracranial response analysis set. Summaries of the number of patients with best objective response in each of the following categories will be provided: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and Non-Evaluable (NE).

Objective response rate and disease control rate will be summarised. For the expansion cohorts, objective response rate will be presented along with 95% exact (Clopper Pearson) confidence intervals.

An additional summary of tumour response for Part B CNS patients will be produced, stratified by previous brain radiotherapy (after undergoing a medical review).

Duration of response

The analysis set for duration of response will be the subset of the evaluable for response population and evaluable for LM response population with a best overall response of confirmed CR/PR.

Duration of response will be summarised and the number (%) of responding patients with a duration of response >3, >6, >9 and >12 months will be presented. If there are sufficient responders, a Kaplan Meier plot and median duration of response (calculated from the Kaplan-Meier) will be presented.

Change in tumour size

The analysis sets for change in tumour size will be the evaluable for CNS response and evaluable for extracranial response. Patients without observed or imputed post baseline target lesion measurements for the visit of interest (week 6, week 12, or all post-baseline visits for best change) will be excluded.

The absolute values and percentage change in target lesion tumour size from baseline will be summarised using descriptive statistics and presented at each timepoint. Best change will also be summarised.

Tumour size will also be presented graphically using waterfall plots, presenting each patient's percentage change in tumour size as a separate bar, with the bars ordered from the largest increase to the smallest decrease. Reference line at the -30% change in tumour size levels will be added to the plots, which corresponds to the definition of partial response.

Progression free survival

The analysis set for PFS will be the evaluable for response. This will only be summarised for the expansion phase as number of patients per cohort will be too small in the escalation phase.

PFS will be displayed using a Kaplan-Meier plot. The number of events, median (calculated from the Kaplan-Meier plot), and proportion of patients without an event at 6 and 12 months will be summarised.

Best BICR assessment via LANO criteria

The analysis set for summarising the best LM BICR assessment will be the evaluable for LM response analysis set. Summaries of the number of patients with best LM BICR assessment in each of the following categories will be provided: Complete Response (CR), Partial Response

(PR), Stable Disease (SD), Progressive Disease (PD) and Non-Evaluable (NE). Other analyses of BICR data may be performed

CSF response rate

The analysis set for CSF response rate will be the evaluable for CSF response.

CSF response rate will be summarised and presented along with 95% exact (Clopper Pearson) confidence intervals.

CSF biochemistry

The analysis set for the assessment of CSF biochemistry will be the CSF biochemstry analysis set. Post-dose glucose and protein levels will be compared with pre-dose using a repeated measures model. Results will be reported as percentage change with 90% confidence intervals.

Assessment of effect of food

The analysis set for the assessment of food will be the food effect population. A Mixed Effects model with treatment (fed/fasted) and period as fixed effects and patient as a random effect will be used to compare AUC/Cmax in the fed state with AUC/Cmax in the fasted state. Log-transformation of exposure measurements AUC/Cmax will be performed prior to analysis. The point estimate and 90% confidence interval for the ratio of geometric means for fed and fasted states will be provided. The geometric mean and its upper and lower confidence limits will be calculated by exponentiation.

Overall survival

Overall survival will be assessed at the data cut-off (DCO) defined as the earlier of 7.5 months after the last patient starts investigational product or 28 days after the final patient discontinues investigational product; a BM or LM patient in Part B will be classed as either alive or dead due to any cause. The time to event will be calculated as the time from first dose until date of death.

A summary of survival status (dead, alive, lost to follow-up, etc) at DCO will be summarized for BM or LM patients. In addition, the number and percentage of patients prematurely censored before data cut-off will be summarized.

Median and quartile survival times will be presented by treatment group, by means of Kaplan-Meier techniques. In addition where data permit, estimates of OS rates and 95% confidence intervals (CIs) from the Kaplan-Meier survival curve will be tabulated. Overall survival by treatment groups will also be plotted. For patients dosed with AZD9291, the analysis will be repeated by T790M status (Unselected, Positive T790M).

Also for patients on AZD9291, a second OS analysis will be assessed at an additional DCO, defined as the 15 months after last patient starts dosing with AZD9291 or 50% OS maturity of AZD9291 T790M+ LM sub-cohort (whichever occurs latest). The second OS analysis may

happen earlier than 15 months if both median OS and median duration of response can be assessed earlier.. This analysis will follow the same as above but will be reported in an addendum to the CSR.

Exploratory biomarker research and pharmacogenetics

If sufficient numbers of patients that will agree to participate in the exploratory biomarker and genetic research, the following formal statistical evaluation will be undertaken. Otherwise only descriptive statistics will be generated.

- CSF biochemistry

Change (and percentage change) from baseline in glucose and protein (in patients with LM) will be modelled using a repeated measures with day as a fixed effect, subject as a random effect and baseline glucose/protein as a covariate. Results will be reported as percentage change with 90% confidence intervals.

- Intra-patient variability of the plasma PK of a single dose of AZD3759

For both AUC and C_{max}, the inter-subject and intra-subject variability (Part B-BM expansion only) will be estimated from the comparison of Day 1 Cycle 0 versus Day 4 Cycle 0. A mixed effects model with Day as a fixed effect and subject as a random effect will be used to calculate covariances for subject and residual. The coefficients of variability percent (CV%) will be calculated from 100* square root (exp(covariance)-1).

Patient Reported Outcomes

Analyses on the EORTC QLQ C-30, QLQ BN-20 and cognition tests will be based on the instruments' scoring manual. Summaries for EORTC QLQ-BN20 and QLQ-C30 will include compliance and change (and percentage change) from baseline for the domains as well as individual items. Speed and accuracy will be summarised for cognitive testing (Part B only).

8. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

8.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes a SAE and is to be reported as such, see Section 6.4.4.**

In the case of a medical emergency the investigator may contact the Study Team Physician. If the Study Team Physician is not available, contact the Study Delivery Team Leader at the AstraZeneca Research and Development.

Name	Role in the study	Address & telephone number

8.2 Overdose

Investigators should 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/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the CRF and on the overdose CRF module.
- An overdose with no associated symptoms is only reported on the overdose CRF module.

If an overdose occurs in the course of the study, then investigators 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, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 28 days.

8.3 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to AstraZeneca using the appropriate forms during the course of the study and within 28 days of the last dose of AZD3759/AZD9291.

8.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study investigational product 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 a pregnancy should be followed up and documented even if the patient was withdrawn from the study.

If a pregnancy occurs during exposure to investigational product or in the *28* days after discontinuing investigational product, then investigators 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 within 1 or 5 days for SAEs, (see Section 6.4.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.2 Paternal exposure

Pregnancy of a patient's partner 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 3 months after dosing ends should be followed up and documented.

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A guide to interpreting the causality QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

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

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

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

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

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

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

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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

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

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix 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 ETHICAL AND REGULATORY REQUIREMENTS

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 the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Ethics and regulatory review

An Ethics Committee should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. This will include approval of the exploratory biomarker and pharmacogenetic research and associated consent(s) forms. The investigator/The Head of the study site will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff. In Japan, the head of the study site will ensure the distribution of these documents to the applicable IRB, and the Principal Investigator to the Investigator and study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study. In Japan, the Head of the study site should submit a notification of direction/determination as well as the Institutional Review Board (IRB) written approval to AstraZeneca. If applicable this approval should clearly state that the exploratory biomarker and pharmacogenetic research is approved.

The Ethics Committee should approve all advertising used to recruit patients 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.

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

Before enrolment of any patient into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators (in Japan, also the Head of the study site) with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the Ethics Committees/Institutional Review Board (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. In Japan, the Head of the study site should submit a written report to the IRB providing the details of all safety relative information reported by AstraZeneca.

Informed consent

Any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation should be described in the informed consent form that is approved by an Ethics Committee.

The Principal Investigator at each centre will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and the optional exploratory biomarker and genetic research component(s)
- Ensure that each patient is notified that they are free to withdraw from the study or the research components at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure each original, signed Informed Consent Form is stored in the Investigator's Study File/medical records
- Ensure a copy of each signed Informed Consent Form is given to the patient

The exploratory biomarker and genetic research component(s) of this study are voluntary and the patient may participate in the main study without participating in the exploratory biomarker and/or genetic research part(s) of the study. To participate in the exploratory biomarker and/or genetic component of the study the patient should sign and date the consent form for the main study and as applicable separate consent forms for the exploratory biomarker and/or the genetic components of the study.

Changes to the protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a Clinical Study Protocol Amendment and where required in a new version of the protocol (Revised Protocol).

The amendment should be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for Revised Protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator. For distribution to Ethics Committee see Section 2.2.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee should 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.

In Japan, study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the study site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a study site's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified by the Principal Investigator. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

Audits and inspections

Authorized 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.

Appendix D DATA AND STUDY MANAGEMENT

Patient 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.

Due to the exploratory nature of the biomarker and genetic research, there will be no routine communication of these results to patients. AstraZeneca will not provide individual results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

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

Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator

Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will visit the study site to review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also to train them in any study specific procedures including collection of samples and the WBDC system utilised. The additional requirements for the collection of the patients' samples for the exploratory biomarker and genetic research will also be clarified.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of the 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 staff members involved in the study (medical, nursing and other staff).

Source data

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

Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study sites, 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 including the specific requirements of the biomarker and genetic research, that data are being accurately and timely recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of the Informed Consent Form(s)of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- If applicable, ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient

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

Data management by AstraZeneca/delegate

Data management will be performed by the .

Data entered in the WBDC system or data captured electronically will be immediately saved to the applicable database and changes tracked to provide an audit trail.

The data collected through third party sources will be obtained and reconciled against study data.

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. All coding will be

performed by the Medical Coding Team at the AstraZeneca Data Management Centre/other party.

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.

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.

Genotype data generated in this study will be stored in the AstraZeneca genotyping Laboratory Information Management System (LIMS) database, or other appropriate secure system, separate from the database used for the main study.

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. The results from this genetic research will be reported separately from the Clinical Study Report for the main study.

Study agreements

The Principal Investigator at each 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 Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, the terms of the Clinical study Agreement shall prevail.

Specific reference to requirements relating to this optional biomarker and genetic research will be included in the study agreement(s).

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

Archiving of study documents

The investigator follows the principles outlined in the Clinical Study Agreement.

End of study

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

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (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 AZD3759.

Appendix E GUIDELINES FOR EVALUATION OF OBJECTIVE TUMOUR RESPONSE USING MODIFIED RECIST 1.1 (RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS) FOR ASSESSMENT OF CNS AND EXTRACRANIAL DISEASE

Introduction

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D6030C00001 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study. The criteria have been modified to allow the separate assessment of CNS and extracranial disease.

Definition of measurable, non-measurable, target and non-target lesions

Patients will be entered to different parts on this study according to the following inclusion criteria

For Part A: (except patients with leptomeningeal disease or measurable brain metastases), at least one measurable extracranial lesion not previously irradiated or biopsied within the screening period, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. Patients with leptomeningeal disease or measurable brain metastases are not required to have measurable extracranial disease

Part A and B (BM): (patients with measurable brain metastases and no leptomeningeal disease), at least one measurable intracranial lesion has progressed or not responded to prior radiotherapy that can be accurately measured at baseline as ≥ 10 mm in the longest diameter by magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. Patients with measurable brain metastases are not required to have measurable extracranial disease.

Part A and B (LM): (patients with leptomeningeal disease), at least one site of CNS leptomeningeal disease that can be accurately assessed by magnetic resonance imaging (MRI) and which is suitable for repeat assessments. Patients with leptomeningeal disease are not required to have measurable CNS or extracranial disease.

In this study CNS disease (brain metastases and leptomeningeal disease) will be assessed separately from extracranial disease using RECIST 1.1 criteria and a separate assessment of CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease).

Progression will be assessed as the visit response if there is progression extracranial disease and/or CNS disease. An overall visit response will be derived by combining the CNS and extracranial disease time point responses.

Measurable:

Extracranial Lesion: A extracranial lesions not previously irradiated or biopsied within the screening period, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. Patients with leptomeningeal disease or measurable brain metastases are not required to have measurable extracranial disease

Brain metastasis: An intracranial brain lesion has progressed or not responded to prior radiotherapy that can be accurately measured at baseline as ≥ 10 mm in the longest diameter by magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. Patients with measurable brain metastases are not required to have measurable extracranial disease.

Non-measurable:

- All other extracranial lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).
- All other intracranial lesions, including small lesions (longest diameter < 10 mm)
- Truly non-measurable lesions include the following: bone lesions, **leptomeningeal disease**, ascites, pleural / pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses /abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated extracranial lesions**
- Previously irradiated intracranial lesions which have not progressed or responded to prior radiotherapy**
- Skin lesions assessed by clinical examination

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

**Localised post-radiation changes which affect lesion sizes may occur

Special Cases:

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

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

Target lesions:

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

Intracranial lesions: A maximum of 5 measurable lesions.

Non-Target lesions:

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

Extracranial and CNS disease (brain metastases and leptomeningeal disease) will be assessed separately.

In addition the investigator will be asked to record an assessment for leptomeningeal disease of complete response, responding, stable or progressing in addition to assessment as part of the non target lesions for CNS response assessment.

Methods of ASSESSMENT

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

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

Table 14 Extracranial disease: 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

Table 14a CNS disease: Summary of Methods of Assessment

Target Lesions	Non-Target Lesions	New Lesions
MRI	MRI	MRI

CT and MRI (extracranial and CNS disease)

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

In the D6030C00001 study it is recommended that CT examinations of the chest and abdomen (including liver and adrenal glands). CT examination with intravenous (i.v.) contrast media administration is the preferred method.

MRI is generally considered to be the best currently available and reproducible method for assessment of CNS disease and for this study to measure TL selected for response assessment and to assess NTL and identification of any new lesions

Clinical examination (extracranial disease only)

In the D6030C00001 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

X-ray (extracranial disease only)

Chest X-ray

In the D6030C00001 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray

In the D6030C00001 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound (extracranial disease only)

In the D6030C00001 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy (extracranial and CNS disease)

In the D6030C00001 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

Tumour markers (extracranial and CNS disease)

In the D6030C00001 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

Cytology and histology (extracranial and CNS disease)

In the D6030C00001 study, histology will not be used as part of the tumour response assessment as per RECIST 1.1.

CSF cytology assessments will be performed and reported separately for the assessment of clinical response for patients with leptomeningeal disease.

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

Isotopic bone scan (extracranial disease only)

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

In the D6030C00001 study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

FDG-PET scan (extracranial disease only)

In the D6030C00001 study FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI

assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

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

Tumour response evaluation

Schedule of evaluation

Imaging assessments will be performed using CT scan of the chest and abdomen (including liver and adrenal glands) at base-line within 28 days of treatments start and then every 6 weeks ± 1week until objective disease progression or withdrawal from study. In addition all patients will have a brain MRI scan at base-line and at follow-up in patients with confirmed brain metastases and/or leptomeningeal disease on the base-line brain scan. In addition additional areas should be investigated based on the signs and symptoms of the patient. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

Target lesions (TL)

Documentation of target lesions (extracranial lesions)

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

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

Documentation of target lesions (intracranial lesions)

A maximum of 5 measurable 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) on the intracranial lesions RECIST eCRF.

All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more 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 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions (extracranial and intracranial lesions)

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

Table 15 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters

Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

Non-Target lesions (NTL)

Evaluation of non-target lesions (extracranial lesions)

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

Evaluation of non-target lesions (CNS lesions)

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

In addition the investigator will be asked to record an assessment for leptomeningeal disease of complete response, responding, stable or progressing in addition to assessment as part of the non-target lesions for CNS response assessment.

Table 16 Evaluation of Non-Target Lesions (extracranial and CNS lesions)

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.

Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

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

New Lesions (extracranial and CNS disease)

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

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

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

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

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

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

Evaluation of Visit Response

The visit response will be derived separately for extracranial and CNS disease separately using the algorithm shown in Table 17.

Table 17 Visit Response (extracranial and CNS disease)

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	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
NA	NA	No	NED

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

Overall visit response

The overall visit response will be using the algorithm shown in Table 18 which is analogous to the RECIST 1.1 approach where brain lesions are assessed as non-target lesions.

Table 18 Overall Visit Response (extracranial and CNS disease)

Extracranial lesion visit response	CNS lesion visit response	Overall response
CR	CR	CR
CR	NA	CR
NA	CR	CR
CR	PR or SD	PR
CR	NE	PR
PR	CR/PR/SD or NE	PR
SD	CR/PR/SD or NE	SD
NA	PR/SD	SD

Table 18 Overall Visit Response (extracranial and CNS disease)

Extracranial lesion visit response	CNS lesion visit response	Overall response
NE	Non PD or NE	NE
NA	NE	NE
PD	Any	PD
Any	PD	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable

Confirmation of response

In the D6030C00001 study, imaging for confirmation of response (CR or PR) for CNS or extra cranial disease should be performed at the next scheduled visit (certainly no less than 4 weeks) following the date the criteria for response were first met.

Central Review

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

REFERENCES

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

Appendix F HY'S LAW

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.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

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:

- Notify the AstraZeneca representative

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

Follow-up

Potential Hy's Law Criteria not met

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

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

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (See Section Actions required when potential Hy's law criteria are met before and after starting study treatment)
- 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 patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver 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

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

Actions required when potential Hy's law criteria are met before and after starting study treatment

This section is applicable to patients who meet PHL criteria on study treatment 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, even if there has been no significant change the patient's condition[#] compared with pre-study treatment visits, the Investigator will:

- Notify the AstraZeneca representative who will inform the central Study Team.

- Follow the subsequent process described is Section Potential Hy's Law Criteria met of this Appendix.

[#] A 'significant' change in the patient's condition refers to a 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. 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.

Actions required for repeat episodes of potential hy's law

This section is applicable when a patient meets PHL criteria on study treatment 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 Actions required when potential Hy's law criteria are met before and after starting study treatment?

If No: follow the process described in Section Potential Hy's Law Criteria met 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 Potential Hy's Law Criteria met of this Appendix

[#] A 'significant' change in the patient's condition refers to a 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. 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.

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 G GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

The use of any natural/herbal products or other "folk remedies" (e.g. Ginseng and other Traditional Chinese Medicine) especially those that are known potent inhibitiors or inducers of CYP3A4 should be discouraged whenever feasible, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications, including those clinically indicated for treatment of adverse events, must be recorded in the eCRF

AZD3759 is an investigational drug for which no data on in vivo interactions are currently available. AZD9291 has limited clinical data available. Based on in vitro data and predicted clinical exposure data for AZD3759 and the in vitro data and limited clinical data for AZD9291, both are is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity.

In vitro data have shown that the principal CYP enzymes responsible for the Phase I metabolism of AZD3759 is CYP 3A4/5. Therefore, drugs strongly inhibiting CYP3A4/5 metabolism are recommended not to be combined with AZD3759. Drugs inducing CYP3A4/5 metabolism should also avoid being combined with AZD3759 if possible.

In vitro data has shown that the principle CYP enzymes responsible for the Phase I metabolism of AZD9291 are CYP2C8 and CYP3A4. Therefore drugs strongly inhibiting CYP2C8 and CYP3A4 are recommended not to be combined with AZD9291. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 2 weeks after the last dose of AZD9291.

If medically feasible, patients taking regular medication, with the exception of potent inhibitors or inducers of CYP3A4, should be maintained on it throughout the study period. Patients may receive any medication that is clinically indicated for treatment of adverse events. Patients taking concomitant medications whose disposition is dependent upon CYP3A4, or CYP2C8 and 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 while receiving AZD9291. Patients taking concomitant medications whose disposition is dependent upon CYP3A4, CYP1A2, CYP2C or p-glycoprotein and which have a narrow therapeutic index should be closely monitored for reduction in therapeutic activity as a result of the reduced exposure of the concomitant medication while receiving AZD9291.

Additionally the following specific guidance will be provided until impact of co-dosing with AZD3759/AZD9291 is understood and can be managed clinically:

Up to 3 fold increase in exposure may occur in statin exposure when coadministered with AZD9291. Such exposure data is not yet available for AZD3759. It is recommended that the starting and maintenance dose of statins should be as low as possible and should be guided by the statin label. Monitoring of low- density lipoprotein (LDL) cholesterol levels is advised. If the patient experiences any potentially relevant adverse events suggestive of muscle toxicity

including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, the statin should be stopped, creatine kinase (CK) levels should be checked, and any appropriate further management should be taken.

AZD3759 is also a P-gp and BCRP inhibitor, which may increase bioavailability of P-gp and BCRP substrate concomitant medications by inhibition of intestinal P-gp and BCRP. Therefore, the plasma level of digoxin, a P-gp substrate, should be closely monitored in this study and its dose may be adjusted appropriately.

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

DRUGS INHIBITING CYP3A4/5 METABOLISAM THAT ASTRAZENECA RECOMMEND ARE NOT COMBINED WITH AZD3759 OR AZD9291

The contribution of Phase I metabolism to the total clearance of AZD3759 or AZD9291 is currently unknown but, to ensure patient safety, the following potent inhibitors of CYP3A4/5 or CYP2C8 must not be used during this study for any patient receiving AZD3759/AZD9291.

Table 19 Drugs inhibiting CYP3A4/5 or CYP2C8

Contraindicated drugs	Withdrawal period prior to AZD3759/AZD9291 start
ketoconazole, itraconazole, indinavir, saquinovir, nelfinavir, atazanavir, amprenavir, fosamprenavir, troleandomycin, telithromycin, fluconazole, nefazodone, cimetidine, aprepitant, miconazole, fluvoxamine, lopinavir, tipranavir, telaprevir, boceprevir, elvitegravir, posaconazole, voriconazole	1 week
Mibefradil	
Conivaptan, Gemfibrozil	
amiodarone	27 weeks
erythromycin, clarithromycin, verapamil, ritonavir, diltiazem	2 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4/5 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

DRUGS INHIBITING CYP3A4/5 METABOLISAM THAT ASTRAZENECA RECOMMEND ARE NOT COMBINED WITH AZD3759 OR AZD9291

To avoid potential reductions in exposure due to drug interactions, the following CYP3A4/5 inducers should be avoided if possible.

Table 20 Drugs inducing CYP3A4/5

Contraindicated drugs	Withdrawal period prior to AZD3759/AZD9291 start
phenytoin, rifampicin, St. John's Wort, carbamazepine, primidone, griseofulvin, barbiturates, troglitazone, pioglitazone, oxcarbazepine, nevirapine, efavirenz, rifabutin, phenobarbital, rifapentin	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 CYP3A4/5 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

Patients should not receive any anti-convulsive drug prophylactically. Anti-convulsive drugs can be given to treat sezures at the discretion of the investigator when necessary.

Dexamethasone, a commonly used steroid to relieve brain edema, is a weak CYP3A4/5 inducer which may increase AZD3759/AZD9291 clearance. Steroid use is allowed in this study but must be recorded in the eCRF.

DURGS 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.

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 AZD3759 or AZD9291. Recommended withdrawal periods following cessation of treatment with these agents are provided in the table.

Table 21 Drugs prolonging QT interval

Contraindicated drug	Withdrawal period prior to AZD3759/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

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 22 Drugs that may prolong QT interval

Drug	Minimum treatment period on medication prior to AZD3759/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

Table 22 Drugs that may prolong QT interval

Drug	Minimum treatment period on medication prior to AZD3759/AZD9291 start
Protriptyline	6 weeks
Tamoxifen	8weeks

Appendix H PATIENT REPORTED OUTCOMES (QLQ C-30)

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	Little	A a Bit	Quite Much	Very
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	Little	A a Bit	Quite Much	Very
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
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

Appendix I PATIENT REPORTED OUTCOMES (QLQ BN-20)

EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Did you feel uncertain about the future?	1	2	3	4
32.	Did you feel you had setbacks in your condition?	1	2	3	4
33.	Were you concerned about disruption of family life?	1	2	3	4
34.	Did you have headaches?	1	2	3	4
35.	Did your outlook on the future worsen?	1	2	3	4
36.	Did you have double vision?	1	2	3	4
37.	Was your vision blurred?	1	2	3	4
38.	Did you have difficulty reading because of your vision?	1	2	3	4
39.	Did you have seizures?	1	2	3	4
40.	Did you have weakness on one side of your body?	1	2	3	4
41.	Did you have trouble finding the right words to express yourself?	1	2	3	4
42.	Did you have difficulty speaking?	1	2	3	4
43.	Did you have trouble communicating your thoughts?	1	2	3	4
44.	Did you feel drowsy during the daytime?	1	2	3	4
45.	Did you have trouble with your coordination?	1	2	3	4
46.	Did hair loss bother you?	1	2	3	4
47.	Did itching of your skin bother you?	1	2	3	4
48.	Did you have weakness of both legs?	1	2	3	4

49.	Did you feel unsteady on your feet?	1	2	3	4
50.	Did you have trouble controlling your bladder?	1	2	3	4

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