AstraZeneca

Revised Clinical Study Protocol

Drug Substance	Selumetinib (AZD6244; ARRY-142886)
Study Code	D1532C00070
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A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Selumetinib (AZD6244; ARRY-142886) in Combination with First Line Chemotherapy Regimens in Patients with Non-Small Cell Lung Cancer (NSCLC)

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AstraZeneca Research and Development site representative

, Study Leader

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

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

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1			

Co-ordinating Investigator

For contact details of AstraZeneca (AZ) personnel see Section 8.1.

INTRODUCTION & STUDY FLOW CHART

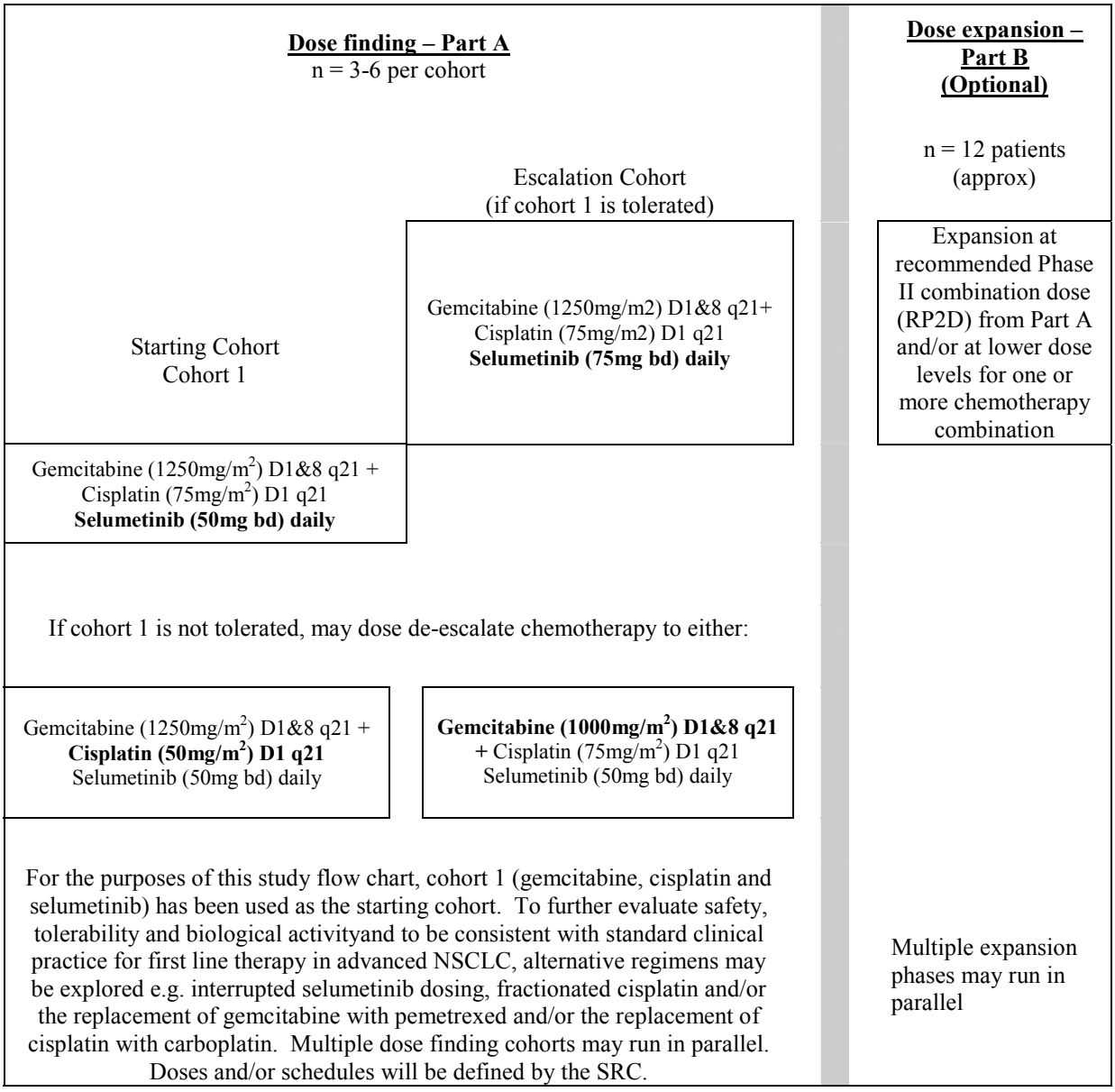
A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Selumetinib (AZD6244; ARRY-142886) in Combination with First Line Chemotherapy Regimens in Patients with Non-Small Cell Lung Cancer (NSCLC)

Selumetinib (AZD6244; ARRY-142886) is an orally available, potent, selective, non-ATP-competitive inhibitor of MEK1/2, licensed for development by AstraZeneca Pharmaceuticals from Selumetinib was discovered by and had the designation ARRY-142886. was responsible for the first-into-human study; the remainder of the clinical development programme for oncology indications is the responsibility of AstraZeneca. AZD6244 Hyd-Sulfate has now been assigned the International Non-proprietary name selumetinib.

This is a Phase I, open-label, multicentre study of selumetinib administered orally in combination with first line chemotherapy regimens to patients with advanced/metastatic NSCLC. The study has been designed to allow an investigation of the optimal combination dose whilst ensuring the safety of patients with intensive safety monitoring.

There are two parts to this study. Part A, Dose finding and an optional Part B, Dose expansion. The option to include Part B will be the decision of the Safety Review Committee (SRC) based on emerging safety and tolerability information from Part A.

Study flow chart



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LIST OF ABBREVIATIONS AND EXPLANATION 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)
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve from zero to infinity
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration
AZ	AstraZeneca
bd	Twice daily
BOR	Best overall response
BRAF	B v-raf-1 murine leukaemia viral oncogene homolog 1
cfDNA	Circulating free DNA
CL	Plasma clearance
CL/F	Apparent oral plasma clearance
C_{max}	Maximum plasma concentration
CPD	Clinical Pharmacology, Drug Metabolism and Pharmacokinetics
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
dFdU	Deoxy-1,1-Difuorouridine
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
ERK	Extracellular signal-regulated kinase
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factors
IATA	International Air Transport Association
IB	Investigators Brochure
ICH	International Committee on Harmonisation
INR	International normalized ratio
IOP	Intraocular Pressure
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LVEF	Left ventrical ejection fraction
MAPK	Mitogen-activated protein kinase
MEK	Mitogen activated protein kinase kinase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multi Gated Acquisition Scan
NCCN	National Comprehension Cancer Network
NE	Not evaluable
NTL	Non-target lesion
NSCLC	Non-small cell lung cancer
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
NYHA	New York Heart Association
OAE	Other significant adverse event
od	Once daily
ORR	Objective response rate
PAD	Pharmacologically Active Dose
PD	Progression of disease
PK	Pharmacokinetics
PR	Partial response
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave

Abbreviation or special term	**Explanation**
QTc	QT interval corrected for heart rate
RAS/RAF/MEK/ERK	Intracellular pathway frequently mutated in cancers
RECIST 1.1	Response Evaluation Criteria in Solid Tumours (version 1.1)
RNA	Ribonucleic Acid
RP2D	Recommended phase II combination dose
SAE	Serious adverse event (see definition in Section 6.4.2)
SD	Stable disease
SRC	Safety Review Committee
TL	Target lesion
ULN	Upper limit of normal
V_{ss}	Volume of distribution
V_{ss}/F	Apparent volume at distribution equilibrium
WBDC	Web Based Data Capture
WHO	World Health Organisation

1. STUDY OBJECTIVES

1.1 Primary objective

To investigate the safety, tolerability and the recommended Phase II combination dose (RP2D) of selumetinib when administered in combination with first line chemotherapy regimens in patients with advanced/metastatic NSCLC.

1.2 Secondary objectives

1. To characterise the steady state pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered with a selected chemotherapy in combination.

2. To characterise the PK of gemcitabine or pemetrexed and cisplatin or carboplatin, when administered in combination with selumetinib.

3. To obtain a preliminary efficacy assessment of selumetinib in combination with a selected chemotherapy in combination by evaluation of tumour response using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (see Appendix F).

1.3 Exploratory objectives

1. To investigate relationships between plasma concentrations/exposure, clinical outcomes, efficacy, adverse events (AEs) and/or safety parameters if deemed appropriate.

2. To explore gene expression signatures/profiles and/or KRAS codon subtypes in tumour and/or tumour derived material that may influence response.

3. To investigate the use of plasma as a potential source of circulating free tumour DNA (cfDNA) for the analysis of KRAS mutation status.

4. To collect a serum sample to assess potential baseline exploratory markers that may predict response to selumetinib.

5. To explore potential biomarkers in optional tumour biopsy samples and/or residual biological samples (e.g. tumour, plasma and/or serum) which may influence development of cancer (and associated clinical characteristics) and/or response and/or the development of resistance to therapy.

6. To collect and store DNA, derived from a blood sample, for future exploratory research into genes/genetic factors that may influence response e.g. distribution, safety, tolerability and efficacy of selumetinib and/or agents used in combination and/or as comparators (optional).

2. BACKGROUND

2.1 Non-Small Cell Lung Cancer (NSCLC)

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total) (GLOBOCAN 2008). NSCLC represents approximately 80% to 85% of all lung cancers). Unfortunately, at the time of diagnosis approximately 70% of NSCLC patients already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of early stage NSCLC patients who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters & Le Chevalier 2005).

A number of molecular abnormalities have been shown to be characteristic of certain lung cancers and where approved treatment is available, guidelines now recommend epidermal growth factor receptor (*EGFR)* mutation testing and anaplastic lymphoma kinase (*ALK*) testing for non-squamous NSCLC. Mutations of the *KRAS* gene are identified in approximately 10 to 30% of advanced NSCLC, mainly in adenocarcinomas (Eberhard et al 2005) but there is not yet an approved treatment for this group of patients. Patients with *EGFR* mutation positive tumours may be treated with an EGFR tyrosine kinase inhibitor, such as gefitinib or erlotinib, while patients with *ALK* positive tumours may receive crizotinib. First-line treatment for patients whose tumours do not have these specific molecular abnormalities usually comprises of a platinum-based doublet chemotherapy which has been shown to prolong survival, improve quality of life, and control symptoms in patients who have a good performance status (NCCN 2012). Despite advances in diagnosis, imaging, staging and treatment, the estimated overall five-year survival for patients with NSCLC in Europe is only 11%, (D'Addario et al 2010), and the median progression free survival for patients receiving first line platinum based doublet therapy is approximately 8 months (Sandler et al 2006).

2.2 Mitogen activated protein kinase kinase (MEK)

Mitogen-activated protein kinase (MAPK) pathways are major signal transduction routes that transfer and amplify messages from the cell surface to the nucleus (Kolch 2000, Schaeffer and Weber 1999). There are several distinct MAPK pathways, including the RAS/RAF/MEK/ERK pathway which regulates cell proliferation, differentiation and survival. Activation of RAS leads to the activation of RAF proteins, which in turn phosphorylate MEK. Phosphorylated MEK then phosphorylate and activate ERK. Activated ERK mediate a range of cellular effects, including cell proliferation. ERK1/2 are the only known substrates of MEK1/2. Thus, inhibition of MEK1/2 as a means to block ERK activation is an attractive strategy for anticancer treatment. Activation of the RAS/RAF/MEK/ERK pathway has been implicated in various cancers, including NSCLC (Khushalani & Adjei 2006). Inhibition of MEK1/2 activity inhibits transduction of the mitogenic and survival signals via RAS/RAF/MEK/ERK regardless of the nature of the upstream activation , resulting in an inhibition on tumour proliferation, differentiation and survival. MEK1/2 activation has also

been implicated in modifying the response to other therapies, both novel and standards of care cytotoxic drugs (Holt et al 2012).

2.3 Selumetinib

Selumetinib is an orally available, potent, selective, non-ATP-competitive inhibitor of MEK1/2, licensed for development by AstraZeneca Pharmaceuticals from Selumetinib was discovered by and had the designation ARRY 142886. was responsible for the first-into-human study; the remainder of the clinical development programme for oncology indications is the responsibility of AstraZeneca. AZD6244 Hyd-Sulfate has now been assigned the International Non-proprietary name selumetinib.

2.3.1 Pre-clinical experience with selumetinib

Testing of selumetinib in a NSCLC cell panel indicates that the cell lines with a growth inhibitory response to MEK1/2 inhibition (sensitive classified as GI50 < 1 μM) tend to carry a pathway related gene mutation, most commonly in *KRAS* (with single examples of *NRAS* and *MEK1* mutation). However, some *KRAS* mutant lung cell lines are also insensitive to monotherapy MEK1/2 inhibition *in vitro*. Published literature also supports the hypothesis that the most MEK1/2 inhibitor sensitive cell lines tend to carry a *BRAF* or *RAS* gene mutation, however this is not an exclusive relationship and cell lines without known RAS/RAF/MEK/ERK pathway associated mutations can show sensitivity to MEK1/2 inhibition (Jing et al 2012, Garon et al 2010, Meng et al 2010).

Selumetinib has demonstrated potent inhibition of xenograft growth both as monotherapy and in combination with a number of cytotoxic and targeted agents. The combination of selumetinib (3 – 12.5 mg/kg bd) with gemcitabine (37.5 – 75 mg/kg twice weekly) has been tested in xenograft models of colorectal and pancreatic cancers, all of which demonstrated a greater tumour growth inhibition by the combination than either agent when administered as monotherapy. The combination of selumetinib (25 mg/kg bd) with cisplatin (3mg/kg once weekly) has been tested in a glioma xenograft in vivo model, and shows a modest trend for improved inhibition of tumour growth of the combination (47.7 % tumour growth inhibition) albeit in a model that is relatively resistant to both monotherapies, tumour growth inhibition of 23.2% and 31.8% for selumetinib and cisplatin respectively. The detailed information on these pre-clinical studies are presented in the selumetinib Investigators Brochure (IB). The combination of selumetinib with carboplatin alone has not been tested in these xenograft models to date.

2.3.2 Clinical experience with selumetinib

Clinical experience with selumetinib as monotherapy and in combination with other anti-cancer agents is described in detail in the IB, including Section 5.4 which lists those adverse events that are to be regarded as expected for regulatory reporting purposes.

Selumetinib 75 mg bd with docetaxel (75 mg/m^2 every 3 weeks) has been investigated as second-line treatment for non-Asian patients with *KRAS* mutation-positive locally advanced or

metastatic NSCLC in a randomised double-blind Phase II study, D1532C00016. A numerically greater increase in overall survival (not statistically significant) was reported in patients receiving selumetinib in combination with docetaxel compared with those receiving placebo in combination with docetaxel, and statistically significant improvements in favour of selumetinib were observed for the secondary endpoints of progression-free survival, objective response rate (ORR) and patients alive and progression free at 6 months (Janne et al 2012). The combination of selumetinib 75 mg bd with docetaxel 75 mg/m^2 was associated with increased toxicity compared with the combination of placebo and docetaxel. However, the safety profile of the combination was generally consistent with the individual monotherapy profiles and the majority of AEs were manageable with appropriate guidance and routine clinical practice.

Selumetinib has not yet been tested in combination with cisplatin, carboplatin, gemcitabine or pemetrexed in patients with advanced NSCLC. In an ongoing Investigator Sponsored Study in patients with advanced biliary tract cancer, the combination of 75 mg bd selumetinib with fractionated cisplatin 25mg/m^2 and gemcitabine 1000mg/m^2 (both agents administered on Days 1 and 8 of each cycle) has been well tolerated for the 28-day initial tolerability evaluation period with no dose-limiting toxicities (DLTs) reported to date at this dose level.

2.4 Combination agents

2.4.1 Gemcitabine

Gemcitabine is indicated for the treatment of bladder cancer, pancreatic cancer, epithelial ovarian cancer, breast cancer and advanced NSCLC. As first line treatment for advanced NSCLC, the recommended combination dose of gemcitabine is 1250 mg/m^2 administered on Day 1 and Day 8 of a 3-weekly treatment cycle. A meta-analysis of 13 randomised Phase II and III trials involving 4556 patients demonstrated a significant reduction in overall mortality in favour of gemcitabine-platinum regimens versus any other platinum containing regimen (HR 0.9, 95% CI: 0.84-0.96) (Le Chevalier et al 2005).

Expected toxicities include bone marrow suppression, nausea, vomiting, raised liver transaminases and alkaline phosphatase, peripheral oedema, haematuria, dyspnoea, alopecia and allergic skin rashes. Please refer to the gemcitabine product information for a complete listing of adverse events associated with administration of gemcitabine. The product information includes advice on dose modification for subsequent cycles according to emerging haematological toxicity. The local gemcitabine product information may vary between countries and should always be confirmed with the local dispensary.

2.4.2 Cisplatin

Cisplatin is indicated for the treatment of a range of advanced or metastatic cancers in monotherapy or combination therapy, including NSCLC. Cisplatin doublet therapy (in combination with gemcitabine) is one of the regimens recommended for first line NSCLC therapy by the National Comprehensive Cancer Network (NCCN 2012). The cisplatin-gemcitabine combination has demonstrated a comparable efficacy outcome in terms of

response rate, median survival time and 1-year survival rate, to three other platinum doublet regimens used for first line therapy in Japanese NSCLC patients (Ohe et al 2007).

Expected toxicities with cisplatin include myelosuppresion, nephrotoxicity, ototoxicity, pyrexia, peripheral neuropathy and cardiac arrhythmias. Please refer to the cisplatin product information for a complete listing of adverse events associated with administration of cisplatin. Hydration must be maintained as per the cisplatin label and local practices. In addition the patient should be advised to drink large quantities of liquids for 24 hours after the cisplatin infusion in order to maintain adequate urine production. The product information includes advice on delaying subsequent dose administration in response to recovery of laboratory parameters. The local cisplatin product information may vary between countries and should always be confirmed with the local dispensary.

2.4.3 Carboplatin

Carboplatin is indicated for the treatment of advanced ovarian cancer of epithelial origin and small cell carcinoma of the lung. Carboplatin doublet therapy (in combination with gemcitabine) is one of the regimens recommended for first line NSCLC therapy by the National Comprehensive Cancer Network (NCCN 2012).

Expected toxicities include myelosuppression, nausea, vomiting, abnormalities in liver function tests, subclinical decrease in hearing acuity, renal toxicity, decreases in serum electrolytes and hyperuricaemia. Please refer to the carboplatin product information for a complete listing of adverse events associated with administration of carboplatin. Premedication with anti-emetics has been reported to be useful for reducing the incidence and severity of nausea and vomiting. The product information includes advice on delaying subsequent dose administration in response to recovery of haematological parameters. The local carboplatin product information may vary between countries and should be confirmed with the local dispensary.

2.4.4 Pemetrexed

Pemetrexed is indicated for the treatment of malignant pleural mesothelioma and advanced NSCLC. A phase III study involving 847 patients with adenocarcinoma histology NSCLC demonstrated that a pemetrexed/ cisplatin regimen (500mg/m2 and 75mg/m2 respectively) showed superior overall survival versus gemcitabine/cisplatin (1250mg/m2 and 75mg/m2 respectively) in patients with adenocarcinoma histology NSCLC (12.6 vs 10.9 months) with better tolerability (Scagliotti et al 2008). Pemetrexed doublet therapy (in combination with cisplatin or carboplatin) is one of the regimens recommended for first line NSCLC therapy by the National Comprehensive Cancer Network (NCCN 2012).

Expected toxicities include neutropaenia, leucopaenia, anaemia, diarrhoea, vomiting, stomatitis/pharyngitis, nausea, anorexia, rash/desquamation and fatigue. Please refer to the pemetrexed product information for a complete listing of adverse events associated with administration of pemetrexed. Premedication with corticosteroids, oral folic acid and an intramuscular injection of Vitamin B12 is recommended in the product information. The

product information also includes advice on dose adjustments and/or delaying subsequent dose administration in response to recovery of haematological parameters or non-haematological toxicities. The local pemetrexed product information may vary between countries and should be confirmed with the local dispensary.

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 selumetinib administered orally in combination with first line chemotherapy regimens to patients with advanced/metastatic NSCLC. The study design allows an investigation of optimal combination dose with intensive safety monitoring to ensure the safety of the patients.

There are two parts to this study. Part A, Dose finding and an optional Part B, Dose expansion. The option to include Part B will be the decision of the SRC based on emerging safety and tolerability information from Part A.

Part A, Dose finding

At least 3 and up to 6 evaluable patients (see section 5.1.6 for definition of an evaluable patient and section 5.1.5 for DLT definition) with advanced/metastatic NSCLC will be enrolled in each cohort in Part A of this study. The total number of patients will depend upon the number of chemotherapy regimens investigated and the number of dose adjustments necessary; if 4 cohorts are required approximately 24 patients will be enrolled in Part A.

In cohort 1, patients will receive gemcitabine (1250 mg/m^2) on Days 1 and 8 plus cisplatin (75 mg/m^2) on Day 1 of each 3-weekly cycle. Patients will commence with selumetinib bd dosing from Day 1 of the cycle. A cycle of treatment is defined as a 3-weekly period, however, it may be longer if the next planned Day 1 chemotherapy infusion is delayed for reasons such as toxicity.

Cohort 1 dosing will begin at 50mg bd selumetinib in combination with chemotherapy. On completion of the DLT assessment period (from the first dose on Cycle 1 Day 1 to before dosing on Cycle 2 Day 1) for cohort 1 the SRC will decide whether to escalate the dose of selumetinib, or reduce the combination dose of gemcitabine or cisplatin for the second cohort.

Selumetinib dosing will commence on Day 1 of the first Cycle and will continue until a treatment or study discontinuation criterion is met.

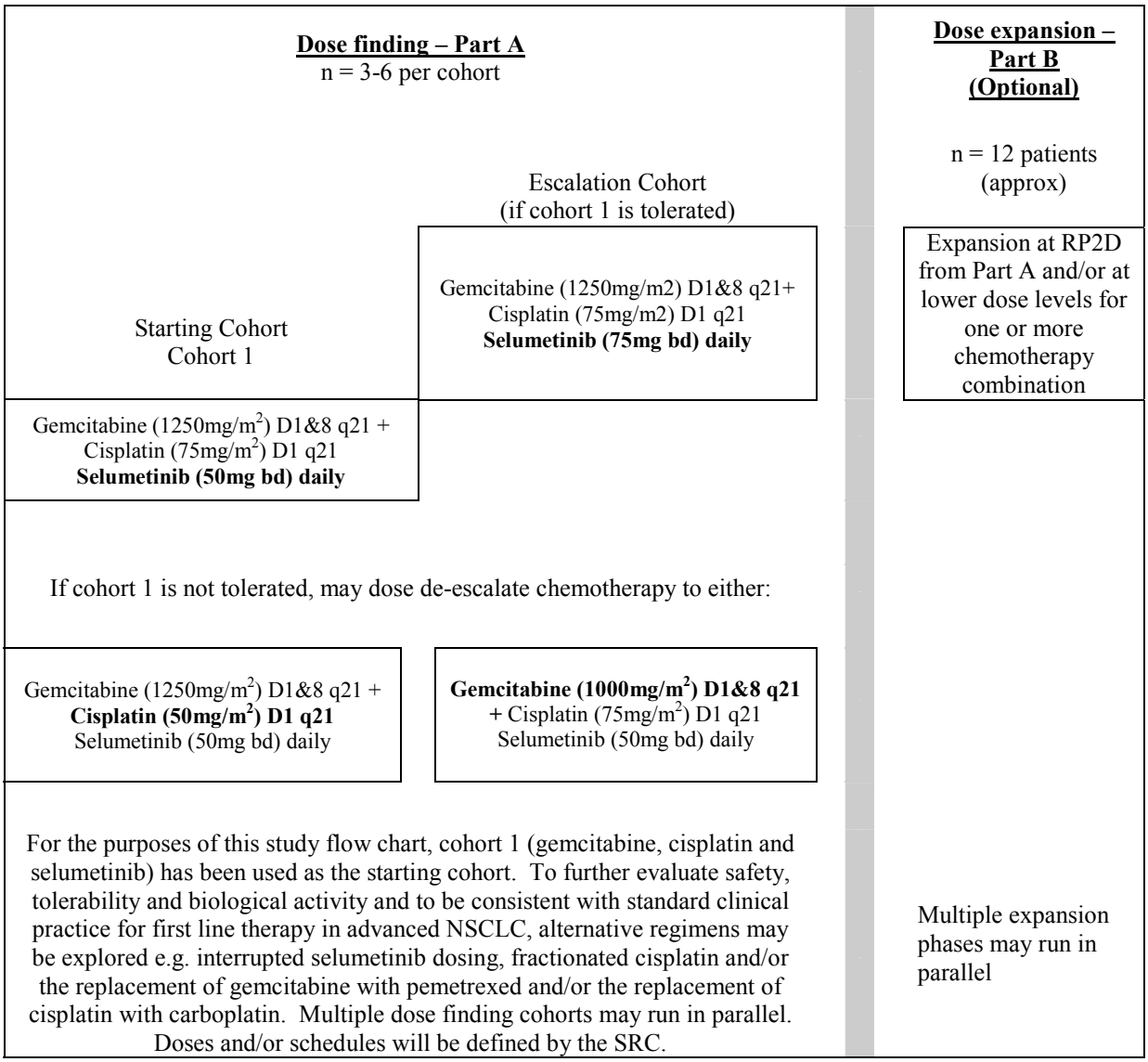
Additional dose levels (not exceeding 1250 mg/m^2 for gemcitabine or 75 mg/m^2 for cisplatin) and/or alternative dosing schedules e.g fractionated cisplatin and/or intermittent selumetinib (Days 2-19 of each 3-weekly cycle) and/or the replacement of gemcitabine with pemetrexed

(dose not exceeding 500 mg/m^2) and/or the replacement of cisplatin by carboplatin (dose not exceeding AUC5) may be explored in Part A to further evaluate safety, tolerability and biological activity of alternative platinum containing doublet regimens. Multiple dose finding cohorts may run in parallel. The dose and dose scheduling of selumetinib administered for each treatment combination may be modified until the MTD has been defined by the SRC. For each treatment combination, the incremental dose increase of selumetinib as agreed by the SRC, will not exceed 25 mg bd.

Part B, Dose expansion

Once a RP2D has been identified from Part A, the SRC may decide to commence Part B if deemed to be necessary. This will include approximately 12 additional evaluable patients at the RP2D defined in Part A and/or lower dose levels, in order to explore further the safety and tolerability of a chemotherapy regimen at these doses. Multiple expansion phases may run in parallel.

Figure 1 Study flow chart



3.2 Rationale for conducting this study and for study design

The combination of selumetinib and a taxane (docetaxel) has been shown to provide clinical benefit with significant improvements in efficacy measures including progression free survival and response rate when given as second line therapy in patients with *KRAS* mutation positive advanced NSCLC (Janne et al 2012). In order to investigate whether clinical benefit may also be derived in patients with treatment naïve advanced NSCLC (i.e. as first line therapy) it is necessary to change the chemotherapy combination agent to be consistent with standard clinical practice in this line of therapy. This study will investigate the combination of selumetinib with the gemcitabine/cisplatin doublet regimen that is one of the options recommended for use as first line therapy in advanced NSCLC (NCCN 2012). This particular

chemotherapy doublet has not been previously tested in combination with selumetinib to date in this clinical setting, therefore this is the first clinical study investigating the combination of selumetinib with gemcitabine/cisplatin in patients with advanced NSCLC. The results from this study will form the basis for decisions for future studies.

Part A of the study (dose finding) will determine the RP2D upon the assessment of the safety and tolerability data collected up until the time of study drug administration on Cycle 2 Day 1. This DLT assessment period was selected as the major toxicities leading to cessation of dose escalation in such studies (haematological, gastrointestinal, liver enzymes) are anticipated to present within this duration, and because the doublet taxane-platinum chemotherapy regimen is administered on a 3-weekly cycle in routine oncology clincial practice. The starting combination doses, dose escalation decision points and cohort size are based upon accepted methodology for phase I oncology studies. The cohort size of at least 3 and up to 6 patients ('rolling six design') has been employed to improve the rate of accrual of patients to cohorts close to the presumed therapeutic dose by reducing the need for late replacement of patients who become non-evaluable during the DLT assessment period, whilst not compromising collection of safety data (Skolnik et al 2008).

To further evaluate safety, tolerability and biological activity and to be consistent with standard clinical practice for first line therapy in advanced NSCLC, the SRC may decide to further adjust the treatment schedules of either the selumetinib (to intermittent dosing) or the cisplatin (to fractionated dosing) or alter the chemotherapy doublet by changing gemcitabine to pemetrexed or changing the platinum containing agent from cisplatin to carboplatin in subsequent cohorts. In all combinations, the dose of each chemotherapy agent investigated will not exceed the product label dose for the NSCLC indication. Multiple dose finding cohorts may run in parallel and each dose combination may continue to be evaluated until the SRC has defined a MTD for selumetinib in each of these combinations. For each treatment combination, the incremental dose increase of selumetinib as agreed by the SRC, will not exceed 25 mg bd.

Part B of the study (dose expansion) may be required to further characterise the safety and tolerability profiles in an additional 12 patients (approximately) at the RP2D and/or lower dose levels, if deemed necessary by the SRC. Multiple expansion phases may run in parallel.

The study population will be patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC who are eligible for standard first line NSCLC chemotherapy regimens. In order to optimally assess the safety and tolerability of the first-line chemotherapy combination regimens, the patients should be chemotherapy treatment naïve for their advanced cancer although prior adjuvant chemotherapy will be permitted if >6 months prior to starting study treatment. In order to also provide a preliminary assessment of efficacy for combination therapy, patients will also be required to have at least one measureable tumour lesion which is suitable for accurate repeated assessment.

Selumetinib, gemcitabine (and/or pemetrexed) and cisplatin (and/or carboplatin) PK data will be collected in the study to assess any gross drug-drug interactions between the agents. The

timings of safety and selumetinib PK assessments in the study have been designed based upon the findings in both pre-clinical studies and clinical monotherapy and combination studies with selumetinib in >1640 patients to date.

Specific safety monitoring and management algorithms will be provided as a separate study aid, "Guidance for Management of Specific Adverse Events in Studies of Selumetinib", detailing how to monitor and manage the occurrence of adverse events and other potential safety signals in this clinical study (see also sections 5.1.8.2 and 6.4).

As part of the clinical drug development program for selumetinib 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 or explain adverse reactions related to drug exposure. 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. The ability to acquire appropriate consent to collect biological samples is of utmost importance in order to establish an archive and allow future meta-analysis of data derived from a number of studies with selumetinib.

AstraZeneca intends to perform genetic research in the selumetinib clinical development programme to explore how host (non-tumour) genetic variations may affect the clinical parameters associated with selumetinib. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and possibly, to genetically guided treatment strategies. Future research may suggest other genes or gene categories as candidates for influencing not only response to selumetinib but also susceptibility to cancer. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

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.

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. If a patient declines to participate in any

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

2. Aged at least 18 years

3. Histological or cytological confirmation of locally advanced (stage IIIB) or metastatic (stage IV) NSCLC who are eligible for standard first-line treatment for NSCLC and unsuitable for radical treatment

4. World Health Organisation performance status 0-1 with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks

5. At least one lesion, not previously irradiated, 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 assessment

6. Patients must be eligible to receive treatment with the platinum doublet combination with which selumetinib is being combined and in accordance with the local product information

7. Females should be using adequate contraceptive measures (see 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

   – Women under 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution

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

8. Male patients should be willing to use barrier contraception i.e. condoms

4.1.1 Host genetics research study (optional)

For inclusion in the optional genetics research study patients must fulfil the following criteria:

1. Provision of optional genetics research informed consent

If a patient declines to participate in the genetics research, there will be no penalty or loss of benefit to the patient. A patient who declines genetics research participation will not be excluded from any other aspect of the main study.

4.1.2 Tumour biopsy at disease progression for exploratory research (optional)

For inclusion in the optional tumour biopsy at disease progression part of the study, patients must fulfil the following criterion:

1. Provision of informed consent for optional tumour biopsy at disease progression

If a patient declines to participate in this research, there will be no penalty or loss of benefit to the patient and they will not be excluded from any other aspect of the main study.

4.2 Exclusion criteria

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

1. Treatment with any of the following:

   - Prior chemotherapy or other systemic anti-cancer treatment (including EGFR TKIs) for advanced NSCLC. Previous adjuvant chemotherapy is allowed, if completed more than 6 months prior to starting study treatment

   - Prior surgery or radiotherapy must be completed more than 6 months before start of study treatment. Palliative radiotherapy must be completed at least 4 weeks before start of study treatment with no persistent radiation toxicity

   - Potent inhibitors or inducers of CYP3A4/5, CYP2C19 and CYP1A2 within 2 weeks of the first dose of study treatment (3 weeks for St John's Wort)

2. With the exception of alopecia, any unresolved toxicities from prior therapy ≥ Common Terminology Criteria for Adverse Events (CTCAE) grade 2

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

4. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, active bleeding diatheses, renal transplant, or active infection including any patient known to have hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required

5. Female patients who are breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control

6. Any of the following cardiac criteria:

- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events (eg, heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age) or mean resting corrected QT interval (QTc) > 470 msec
- Uncontrolled hypertension (BP≥150/95 mmHg despite medical therapy)
- Acute coronary syndrome within 6 months prior to starting treatment
- Angina Canadian Cardiovascular Society Grade II-IV (despite medical therapy)
- Symptomatic heart failure (New York Heart Association [NYHA] II-IV)
- Prior or current cardiomyopathy
- Baseline left ventrical ejection fraction (LVEF) <55% measured by echocardiography or Multi Gated Acquisition Scan (MUGA). Appropriate correction to be used if a MUGA is performed.
- Atrial fibrillation with a ventricular rate >100bpm at rest
- Severe valvular heart disease

7. Any of the following ophthalmological criteria:
   - Current or past history of central serous retinopathy or retinal vein occlusion
   - Intraocular pressure >21mmHg
   - Uncontrolled glaucoma (irrespective of intraocular pressure [IOP])
8. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
   - Absolute neutrophil count < 1.5 x 109/L
   - Platelet count < 100 x 109/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
- Creatinine clearance < 50 ml/min (calculated by Cockcroft and Gault equation)

9. History of another primary malignancy within 5 years prior to starting study treatment, except for adequately treated basal or squamous cell carcinoma of the skin or cancer of the cervix in situ and the disease under study.

10. 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

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

12. Any contraindication to the combination chemotherapy as per local prescribing information

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

1. Previous allogeneic bone marrow transplant

2. 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. Females of child-bearing potential should use reliable methods of contraception from the time of screening until 4 weeks after discontinuing study treatment or longer if required for the combination chemotherapy agents. Selumetinib should not be administered to pregnant or breast-feeding women and conception while on treatment must be avoided. Reliable methods of contraception should be used consistently and correctly. Acceptable methods of contraception for selumetinib include implants, injectables, combined oral contraceptives, some intrauterine devices/systems and sterilisation including vasectomy of the partner (which must all be combined with barrier methods of contraception). Sexual abstinence is also an acceptable method of contraception according to international recommendations. For the combination chemotherapy agents, the reliable methods of contraception should be as per the national label for each agent.

2. Male patients with sexual partners who are pregnant or who could become pregnant (i.e. women of child-bearing potential) should use acceptable methods of contraception during the trial and for a washout period of 12 weeks after the last dose of selumetinib or longer if required for the combination chemotherapy agents. Reliable methods of contraception should be used consistently and correctly. Acceptable methods of contraception for selumetinib include the use of condoms, spermicidal foams or prior vasectomy. Sexual abstinence is also an acceptable method of contraception according to international recommendations. For the combination chemotherapy agents, the reliable methods of contraception should be as per the national label for each agent.

3. Patients should avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated.

4. Patients should avoid the ingestion of large amounts of grapefruit and Seville oranges (and other products containing these fruits, e.g. grapefruit juice or marmalade) during the study.

5. Selumetinib capsules contain D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS, a water-soluble form of vitamin E) as an excipient. Therefore:

   – The maximum dose of vitamin E patients may receive from selumetinib is approximately 210 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided in patients receiving the capsule formulation.

   – High dose of vitamin E have been reported to potentiate the anticoagulant activity of coumarins such as warfarin. Patients who are taking coumarin anticoagulants should increase the frequency of assessment of anticoagulation, such as International Normalised Ratio (INR) measurements, upon initiation of dosing with selumetinib.

6. Patients should not donate blood during the study and for 3 months following the last dose of study medication.

7. Patients should be made aware of the need for oral care during the study. Refer to the separate study aid “Guidance for Management of Adverse Events in Studies of Selumetinib”.

Investigators should also note specific restrictions relating to the combination agent according to the local prescribing information.

For restrictions relating to concomitant medications see next Section 4.3.1.

4.3.1 Concomitant treatments

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded on the Case Report Form (CRF) in the web based data capture system (RAVE).

No other anti-cancer agents or investigational drugs (other than the protocol defined combination chemotherapy) should be administered whilst patients are receiving selumetinib. The Investigator can initiate any subsequent anti-cancer therapy only after the patient has discontinued selumetinib.

Throughout the study, patients should avoid changes to, or the addition of, all concomitant medications, in particular any that may affect the metabolism of selumetinib (e.g. CYP1A2, CYP2C19 or 3A4 inhibitors/inducers), unless considered clinically indicated. Investigators should also note specific restrictions relating to the chemotherapy combination agents according to the local prescribing information.

Granulocyte colony stimulating factors (GCSF) should not be used prophylactically during Cycle 1.

Supportive care and other medications that are considered necessary for the patient's well-being, such as prophylactic antibiotics for patients with central obstructing lesions, may be given at the discretion of the Investigator.

5. STUDY TREATMENT AND CONDUCT

5.1 Treatment

5.1.1 Selumetinib

Selumetinib will be administered orally bd.

The investigational product will be supplied by AstraZeneca as 25mg capsules in bottles of 60 capsules. Additional information about the investigational product may be found in the IB.

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.

The label will include the following information:

Study code, unique medication ID number, expiry date, contents of the bottle, dosing instructions and storage conditions. The labels will have blank spaces for the site personnel to complete the following at the time of drug dispensing: enrolment code, visit number and dispensing date.

Each bottle of selumetinib capsules will have a tear-off portion that will be removed at the time of dispensing and attached to the Drug Label Accountability Log.

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

At each dispensing visit, sufficient selumetinib for 3 weeks treatment, plus overage, will be dispensed. The number of capsules provided may be reduced in the event of a required dose reduction (see Table 2).

In Cohort 1, patients should swallow two selumetinib 25 mg capsules bd, commencing on Day 1. Capsules should be taken whole and with approximately 240 mL water.

In subsequent cohorts the number and dosing regimen for capsules of selumetinib to be taken will be determined by the SRC.

All doses of selumetinib should be taken on an empty stomach (no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing).

The dose should be taken at approximately the same time each morning and evening +/- 1-2 hours. The minimum interval between doses should be 10 hours and the maximum interval should be 14 hours. On the clinic day on which PK samples are scheduled to be taken the dosing should be delayed until arrival at the clinic and until the pre-dose PK sample has been taken; patients should not take their dose until instructed to do so by the Investigator/Study Nurse.

Wherever possible, doses should not be missed. If a patient misses taking a scheduled dose, they should take the next dose at the next scheduled time and the missed dose will not be made up. If a patient vomits after taking their selumetinib medication, they should not make up for this dose, but should take the next scheduled dose.

Patients will be provided with dosing instructions for the study.

5.1.2 Chemotherapies

Chemotherapies will be sourced locally and dispensed by the pharmacist to meet the requirements of local procedures and the specific chemotherapy product information.

Dose reductions are to be performed as per local procedure and specific chemotherapy product information. Any deviations from dosing schedule, dose interruptions, or dose reductions should be recorded in the eCRF.

5.1.3 Starting doses, combination dose finding scheme and stopping criteria

In Cohort 1 dosing will begin at 50 mg bd selumetinib on Day 1 in combination with gemcitabine (1250 mg/m^2) on Days 1 and 8 plus cisplatin (75 mg/m^2) on Day 1 of each 3-weekly cycle.

Patients will be enrolled to ensure a minimum of 3 and a maximum of 6 evaluable patients per cohort. Combination dose finding will follow the scheme below, according to the following logic:

- If no DLT is observed (for definition see Section 5.1.5) within a cohort of 3-6 evaluable patients then dose escalation may occur. Dose increases may only be permitted after review of data from a minimum of 3 evaluable patients has been performed.
- If one patient experiences a DLT in a group of 3 or more evaluable patients then the cohort will be expanded to include 6 evaluable patients. If only one DLT is observed in the complete cohort of 6 evaluable patients then dose escalation may occur.
- If 2 or more patients experience a DLT in a group of up to 6 patients, irrespective of the number of patients enrolled, the combination dose will be considered not tolerated and recruitment to the cohort and dose escalation will cease. A de-escalation of one component of the combination regimen may be considered in order to better define the MTD of selumetinib and the RP2D for this treatment combination (see section 5.1.5.1 and 5.1.5.2.)

The potential combination dose options for investigation are presented in Table 1.

Table 1 Potential combination dose finding options[1]

Dose level	Dose of selumetinib mg to be administered bd	Dose of gemcitabine mg/m^2 to be administered on Days 1 and 8 each cycle	Dose of cisplatin mg/m2 to be administered on Day 1 each cycle
+1	75	1250	75
1	50	1250	75
-1A[2]	50	1250	50
-1B[2]	50	1000	75

[1] Treatment combinations and dose options for selumetinib will be agreed by the SRC however the dose of each chemotherapy agent investigated will not exceed the product label dose for the NSCLC indication.
[2] Option A or B will depend on assessment of which chemotherapy agent is the major source of observed toxicity in previous cohort by the SRC.

The decision to investigate any iterations of these combinations or 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 5.1.7). Furthermore the SRC may decide to explore further cohorts including intermittent selumetinib dosing (Days 2-19 of each 3-weekly cycle), or the replacement of gemcitabine with pemetrexed (fractionated cisplatin (25mg/m^2 on Days 1 and 8 of each 3-weekly cycle), or the replacement of gemcitabine with pemetrexed (500mg/m^{2}on Day 1 of

each 3-weekly cycle), or the replacement of cisplatin with carboplatin (AUC5) if deemed necessary to determine a RP2D.

For starting cohorts in Part A exploring alternative chemotherapy regimens, the SRC may decide to proceed with a starting dose for selumetinib of 75mg bd after review of safety and tolerability data from previous cohorts.

There will be no intra-patient dose escalations.

There are no specific individual PK stopping criteria included in this study. Guidance for dose modifications for the management of specific AEs will be provided as a separate study aid for the Investigators.

5.1.4 Dose expansion

Once the RP2D is defined in Part A, if required the SRC may decide to conduct a dose expansion phase, Part B, at the defined RP2D and/or lower dose levels, in order to refine the safety and tolerability of the combination regimen. Additional patients will be enrolled to ensure approximately 12 further patients complete the first 3-weekly cycle of assessments. The patients will have the same treatment schedule and all other assesments performed at the same timepoints as in Part A. There will be no specific stopping criteria for Part B of the study, however, the emerging data from the expansion phase will be monitored regularly by the SRC. Multiple expansion phases may run in parallel for alternative chemotherapy regimens and/or dose levels.

5.1.5 Definition of dose-limiting toxicity

A DLT is defined as any toxicity not attributable to the disease or disease-related processes under investigation, which is considered related to the combination of chemotherapy plus selumetinib, which occurs any time from the first dose on Cycle 1 Day 1 up until the time of dosing on Cycle 2 Day 1 and is dose limiting and which includes:

1. Haematological toxicity ≥ CTCAE grade 4 present for more than 4 days

2. Non-haematological toxicity ≥ CTCAE grade 3 including:

   - Febrile neutropenia (Grade ≥3 low neutrophil count with temperature of > 38.3°C on a single reading or with a sustained temperature > or equal to 38°C for more than one hour)

   - QTc prolongation (> 500 msec)

3. Any toxicity that results in a disruption of selumetinib or chemotherapy dosing schedules of more than 14 continuous days (if the inability to resume chemotherapy is considered independent of selumetinib therapy, the adverse events will not constitute a DLT)

4. Any other toxicity that is greater than that at baseline, is clinically significant and/or unacceptable, does not respond to supportive care, that is judged to be a DLT by the Safety Review Committee

A DLT excludes:

1. Alopecia of any grade

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

5.1.5.1 Definition of recommended Phase II combination dose

A combination dose will be considered non-tolerated if 2 or more of up to 6 evaluable patients experience a DLT at the combination dose level. Six evaluable patients are required to determine the combination RP2D.

5.1.5.2 Definition of maximum tolerated dose

A dose will be considered non-tolerated and dose escalation will cease if 2 or more patients in a group of up to 6 evaluable patients experience a DLT at a dose level. Once the non-tolerated dose is defined the MTD of selumetinib in combination with each regimen will be confirmed at the previous dose-level below the non-tolerated dose or a dose between the non-tolerated dose and the last tolerated dose may be investigated. Six evaluable patients are required to determine the MTD.

5.1.6 Definition of evaluable patient

For decisions on cohort tolerability, an evaluable patient is defined as a patient that has received selumetinib and chemotherapy and either:

has completed minimum safety evaluation requirements and has received at least 75% of the specified dose of selumetinib during the period from Cycle 1 Day 1 to before dosing on Cycle 2 Day 1

or

has experienced a DLT during the period from first dose administered on Cycle 1 Day 1 up until the time of dosing on Cycle 2 Day 1

5.1.7 Safety Review Committee

After the completion of each cohort during the dose finding phase of the study, the SRC will evaluate the safety and tolerability of the combination of selumetinib and chemotherapy to decide the next step.

The SRC will be responsible for the following:

- Assessment of all available safety, tolerability, efficacy, exposure and PK data during the course of the study
- All decisions regarding further cohorts, including dose escalation, dose de-escalation, change of selumetinib dose schedule or confirmation of MTD, fractionation of cisplatin, change of gemcitabine to pemetrexed, change of platinum agent or cessation of dosing
- All decisions for the replacement of any excluded patients on study, if necessary
- Determination of the RP2D combination from Part A to assess in a Part B dose expansion if required for further evaluation
- Defining Patients who have experienced DLTs per Clinical Study Protocol definition

The SRC will consist of:

- AZ Study Team Physician, who will chair the committee, or delegate
- Principal Investigator or delegate from each Part A investigational site

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

- AZ Global Safety Physician or delegate
- AZ Medical Science Director or delegate
- AZ Senior Physician from another project

The AZ Study Pharmacokineticist, AZ Study Statistician, AZ Patient Safety Scientist, AZ 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. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

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 to make a decision on the dose for the next cohort of patients. Any dose interruptions and reductions will be taken into account.

The decision may be to:

1. Expand the cohort to a maximum of 6 evaluable patients

2. Escalate the dose of selumetinib or define the MTD

3. De-escalate the dose of gemcitabine or cisplatin to a lower dose level

4. Modify dosing combinations e.g. change to intermittent dosing of selumetinib, change to fractionated dosing of cisplatin, replace gemcitabine with pemetrexed, replace cisplatin with carboplatin

5. Stop the dose finding part of the study

6. Commence Part B for the combination

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 patient should be included or excluded in the dosing decisions for the associated treatment group.

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.

In Part B (expansion phase) the SRC will continue to monitor safety and will agree any action needed to define the dose or dosing schedules.

5.1.8 Management of study treatment related toxicity

The immediate management of any adverse events should be according to standard clinical practice for that event; for example anaemia should be managed by blood transfusion and hypertension should be treated with appropriate anti-hypertensive medication. Subsequent management of treatment related adverse events should be guided by the Investigators' assessment of causality

5.1.8.1 Dose modifications to selumetinib

Treatment with selumetinib 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 selumetinib:

- Any intolerable adverse event regardless of grade

- Any adverse events ≥ CTCAE Grade 3 (despite optimal supportive care)

– A DLT

If the toxicity resolves to CTCAE Grade 1 (Grade 2 for rash) or baseline within 14 days of onset and the patient is showing clinical benefit, treatment with selumetinib may be restarted at the original dose or the dose may be reduced using the dose modification guidance below (See Table 2) at the discretion of the Investigator.

If a further episode of the same AE subsequently requires dose interruption, selumetinib must be restarted at the next dose modification level down on improvement of the AE.

If a different AE subsequently requires dose interruption, selumetinib may be restarted at at the same dose or the next dose modification level down on improvement of the AE at the discretion of the Investigator.

Table 2 Selumetinib dose modification guidance for toxicity[1]

Dose level prior to toxicity	Modified dose level
75 mg bd	75 mg od
75 mg od	50 mg bd
50 mg bd	50 mg od
50 mg od	Permanent discontinuation

[1] For doses of selumetinib above 75mg bd, the same dose reduction principles and guidance should apply e.g. initial dose reduction of 'bd' dose to 'od' dose; second dose reduction of 25mg, administered bd.

If the selumetinib toxicity does not resolve to CTCAE Grade 1 (grade 2 for rash) or baseline after 14 days, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

No re-escalation of selumetinib dose is permitted in this study.

All dose delays, reductions and modifications will be recorded in the appropriate electronic case report form (eCRF).

5.1.8.2 Management and investigation of specific AEs

Recommendations for the management or investigation of the following specific AEs is provided as a separate study aid in the "Guidance for Management of Adverse Events in Studies of Selumetinib":

- Rashes
- Diarrhoea

- Reduction in LVEF
- Dyspnoea
- Visual disturbances
- Oral Care

5.1.8.3 Dose modifications to chemotherapy

All monitoring and management of chemotherapy-related toxicities should be in accordance with the national prescribing information and standard site practice. If the next cycle of chemotherapy is delayed, for the resolution of chemotherapy-only related toxicity, administration of selumetinib should continue without interruption. If selumetinib is dosed on an intermittent dosing regimen (Days 2-19 each cycle) and the next cycle of chemotherapy is delayed, for the resolution of chemotherapy-only related toxicity, administration of selumetinib should be re-started and continued without interruption until 2 days prior to the next planned administration of chemotherapy, as guided by the rate of resolution of the chemotherapy related toxicity.

All dose delays, reductions, and modifications will be recorded in the appropriate electronic case report form (eCRF).

5.1.9 Duration of therapy

Patients may continue to receive selumetinib as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria. This also applies to patients who discontinue one or both combination chemotherapy agents, who may continue to receive selumetinib in combination with the remaining component of the combination regimen or as monotherapy.

Patients are expected to receive up to 6 cycles of the combination doublet chemotherapy in the absence of significant toxicity. Investigators may decide to reduce the number of cycles of one or both combination chemotherapy agents if significant toxicity develops. Further cycles of chemotherapy may also be administered at the Investigator's discretion if they feel it to be beneficial and it does not contravene local practice.

5.1.10 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 eCRF.

Diary cards detailing the dosing schedule will be provided to the patients when they start selumetinib dosing. Patients will be asked to record their daily doses of selumetinib in the diary card during Cycle 1. The diary card will be returned to AstraZeneca in order to monitor compliance and aid PK data interpretation. The data from the diary card will not be validated and will not be data-based.

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 for appropriate destruction. Certificates of delivery and destruction should be signed.

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

The selumetinib starting dose of 50 mg bd was selected as it is 2/3rds of the combination dose which was used in the Phase II study D1532C00016 which tested the combination of selumetinib plus docetaxel as 2nd line therapy in patients with advanced NSCLC (Janne et al 2012), and in another recent Phase II study which investigated the combination of selumetinib with dacarbazine in patients with advanced melanoma (D1532C00006). Should the first line chemotherapy combination be demonstrated to be tolerated in a minimum of 3 patients with no DLTs, the selumetinib dose will be escalated as described in Section 5.1.3. This will ensure that the fewest possible patients are exposed to selumetinib below a previously identified efficacious chemotherapy combination dose.

The doublet chemotherapy combination of gemcitabine (1250 mg/m^2) on Days 1 and 8 plus cisplatin (75 mg/m^2) on Day 1 of each 3-weekly cycle was selected as it is used for first line therapy in patients with advanced NSCLC (Ohe et al 2007, NCCN 2012). The triplet combination of selumetinib, gemcitabine and cisplatin has never previously been tested in patients with NSCLC, therefore if a dose level is determined to be not tolerated the decision will be taken by the SRC as to which agent in the combination should be dose adjusted in the next cohort, based upon clinical judgement as to what is the predominant contributor to the dose limiting toxicities. The doses of gemcitabine and cisplatin in this study will not exceed 1250 mg/m^2 and 75 mg/m^2 respectively, to be consistent with the product labels for use in the NSCLC indication. The dose and dose scheduling of selumetinib administered for each treatment combination may be modified until the MTD has been defined by the SRC. For each treatment combination, the incremental dose increase of selumetinib as agreed by the SRC, will not exceed 25 mg bd.

To further evaluate safety, tolerability and biological activity and to be consistent with standard clinical practice for first line therapy in advanced NSCLC, the SRC may decide to adjust scheduling of selumetinib or cisplatin, change gemcitabine to pemetrexed or change cisplatin to carboplatin. Selumetinib may then be administered in an intermittent schedule from Days 2-19 of each treatment cycle in order to provide a washout period around Day 1 of each cycle when the platinum agent (cisplatin or carboplatin) is administered. Non-clinical studies investigating the scheduling of the combination of selumetinib with a taxane in a *KRAS* mutant colorectal xenograft model, HCT116, indicated that an intermittent administration of selumetinib around the chemotherapy dose resulted in no difference in the observed tumour growth inihibition compared with a continuous administration regimen (AstraZeneca data on file). Therefore an intermittent dosing schedule of selumetinib should not affect potential efficacy but may contribute in reducing combination toxicity. Fractionating the administration of cisplatin to Days 1 and 8 of each cycle, in combination

with selumetinib and gemcitabine, has demonstrated an acceptable tolerability profile in an ongoing Investigator Sponsored Study in advanced biliary tract cancer. Carboplatin is used clinically as an alternative platinum in first line NSCLC doublet chemotherapy regimens when tolerability of cisplatin may be an issue (NCCN 2012). Similarly, pemetrexed is used clinically as an alternative to gemcitabine in the platinum doublet regimen in patients with an adenocarcinoma NSCLC histology (Scagliotti et al 2008).

The combination dose-finding criteria have been set in accordance with traditional oncology phase I study methodology, employing regular review of all available data by an SRC. Selumetinib has been administered to > 1640 patients to date. There are no specific individual PK stopping criteria included in this study. Additional non-specific criteria for discontinuation from the study are described in Section 5.4 of this protocol. Guidance for dose modifications for the management of specific AEs will be provided as a separate study aid for the Investigators.

5.3 Benefit/risk and ethical assessment

The combination of selumetinib with docetaxel has been shown to potentially provide improved clinical outcome when used as second line therapy in patients whose NSCLC tumours harbour *KRAS* mutations, in a Phase II study (Janne et al 2012). The combination of selumetinib with docetaxel was less well tolerated compared to placebo in combination with docetaxel, although there was no increase in deaths resultant from the adverse events. Preclinical and clinical data suggest that activity of the combination of selumetinib plus docetaxel may not be dependent on the presence of a *KRAS* mutation in all tumour models. For further information on completed selumetinib studies please refer to the IB. This study will investigate the combination of an alternative chemotherapy regimen with selumetinib in order to extend the clinical indication into first line therapy setting. The study will be performed in patients with advanced NSCLC whose tumours are not selected for specific *KRAS* mutation status, although this information will be sought retrospectively. Gemcitabine (and pemetrexed) and cisplatin (and carboplatin) are agents recommended for use as first line therapies for patients with advanced NSCLC (NCCN 2012), therefore patients participating in this study will still receive standard of care treatment in addition to selumetinib.

The emerging safety profile has not identified any risks that would preclude investigation of selumetinib in the advanced NSCLC setting. Based on the identified and potential risks associated with treatment, this clinical study protocol incorporates mandatory safety monitoring procedures and additional guidance documents to assist with early diagnosis and rapid management of potential drug-related symptoms (echocardiograms/MUGA, ophthalmological exams, rash management, dyspnoea, LVEF reduction algorithm). Dose modification algorithms based on previous clinical studies are also included in this clinical study protocol. The management of toxicities related to the chemotherapy combination agents will be according to the local prescribing information.

In summary, the evidence of clinical anti-tumour activity in patients with advanced NSCLC receiving selumetinib in combination with chemotherapy, and the manageable combination

toxicity profile in second line patients, suggest an acceptable benefit-risk profile for selumetinib, which warrants investigation in first line NSCLC setting.

5.4 Discontinuation of investigational product and withdrawal from study

Patients may be discontinued from selumetinib and/or combination chemotherapy 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 (please refer to 'Guidance for Management of Specific Adverse Events in Studies of Selumetinib')
- Severe non-compliance to this protocol as judged by the Investigator and/or AstraZeneca
- Objective disease progression, based on RECIST 1.1 evaluation
- Patients incorrectly initiated on study medication (Section 5.4.1)
- Risk to patients as judged by the Investigator and/or AstraZeneca
- Maximum number of cycles reached based on standard hospital practice (combination chemotherapy only)

Patients who discontinue one or both combination chemotherapy agents may continue to receive selumetinib in combination with the remaining component of the combination regimen or as monotherapy, if in the opinion of the Investigator, they are continuing to derive clinical benefit and in the absence of any discontinuation criteria.

Any patient who permanently discontinues selumetinib will continue on study for a 28 day safety follow up period and then will be withdrawn from the study (Section 5.4.2). Patients who remain on combination chemotherapy once selumetinib is discontinued will be managed in accordance with standard local practice and will have no further study specific assessments.

Patients that are withdrawn from the study but are evaluable for an SRC dose escalation decision as per the definition in Section 5.1.6 will not be replaced. Any patient that is withdrawn from Part A and is not evaluable for an SRC dose escalation decision will be replaced to ensure a minimum number of evaluable patients.

Patients may withdraw from any aspects of the voluntary exploratory research (see Section 6.7) 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 6.8.5.

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 study criteria are enrolled in error, incorrectly started on treatment, or where patients subsequently fail to meet the criteria for the study post enrolment, a discussion must occur between the AZ Study Team Physician and the Investigator regarding the patient's safety and well-being and whether to continue or discontinue the patient from the study treatment. The AZ Study Team Physician is to ensure all such decisions 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 6.3.11). Adverse events should be followed up (see Sections 6.3.11, 6.4.3 and 6.4.4) and study drug should be returned by the patient.

5.5 Study timetable and end of study

The study is expected to start in Q1 2013.

There will be a data cut-off defined as the earlier of 12 (±1) weeks after the last patient recruited starts investigational product or 28 days after the final patient discontinues investigational product. Data analysis will be performed and a Clinical Study Report (CSR) written based on this data set.

Any patients still receiving study treatments at the time of data cut-off will be able to continue to receive selumetinib 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 selumetinib (see Section 6.4.4). No other assessments will be performed for the purposes of the study. Further patient assessments will be managed in accordance with standard local practice.

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

Drug Accountability information for selumetinib must still be collected until all patients have completed treatment.

6. STUDY PLAN AND COLLECTION OF STUDY VARIABLES

6.1 Study Plan

Table 3 Study Plan – Continuous Selumetinib Dosing (Gemcitabine Day 1 & 8 and Cisplatin Day 1)

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Discontinuation from selumetinib**		**Section**
Visit Description	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5 & beyond (additional visits every 3 weeks)**	**Selumetinib Discontinuation Visit**	**Final follow up 28 days post last dose of selumetinib**	
Day	**-28 to –1**	**1**	**8**	**15**	**22/1**	**43/1**	**64/1**	**85/1**	**N/A**	**N/A**	
Week	**-4 to 0**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**N/A**	**N/A**	
Visit Window (compared to Day 1)	**N/A**	**N/A**	**±2 days**	**±2 days**	**±2 days**	**±1 wk**	**±1 wk**	**±1 wk**	**N/A**	**±7 days (compared to treatment disc visit)**	
Informed consent	X										4
Provision of archival tumour material (tissue/cytology), if available (any time during the study)		→									6.7.1.1
Screening procedures (incl medical and surgical history, demography, smoking status)	X										4.3.1 6.3.1
Anti-cancer treatment	X									X	6.3.1 6.3.11
Optional genetic consent & sample		X									6.7.2
cfDNA Plasma sample		X									6.7.1.2
Serum sample for exploratory biomarker analysis		X									6.7.1.2

Table 3 Study Plan – Continuous Selumetinib Dosing (Gemcitabine Day 1 & 8 and Cisplatin Day 1)

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Discontinuation from selumetinib**		**Section**
Visit Description	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5 & beyond (additional visits every 3 weeks)**	**Selumetinib Discontinuation Visit**	**Final follow up 28 days post last dose of selumetinib**	
Day	**-28 to –1**	**1**	**8**	**15**	**22/1**	**43/1**	**64/1**	**85/1**	**N/A**	**N/A**	
Week	**-4 to 0**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**N/A**	**N/A**	
Visit Window (compared to Day 1)	**N/A**	**N/A**	**±2 days**	**±2 days**	**±2 days**	**±1 wk**	**±1 wk**	**±1 wk**	**N/A**	**±7 days (compared to treatment disc visit)**	
Adverse events	X	→									6.4
Concomitant medications	X	→									4.3.1 6.3.11
Vital signs (including height at baseline), weight	X	X	X	X	X	X	X	X	X	X	6.3.3
Concomitant procedures		X	X	X	X	X	X	X	X	X	6.3.10
Clinical chemistry/haematology	X	X	X	X	X	X	X	X	X	X	6.3.5
Urinalysis	X										6.3.5
Pregnancy test (pre-menopausal females only)	X	(X)	as clinically indicated →								6.3.6
Plasma sample collection for selumetinib PK			X		X						6.5.1
Plasma sample collection for gemcitabine PK			X		X						6.5.1
Plasma sample collection for cisplatin PK					X						6.5.1
Echocardiogram/MUGA	X							X		(X)	6.3.7

Table 3 Study Plan – Continuous Selumetinib Dosing (Gemcitabine Day 1 & 8 and Cisplatin Day 1)

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Discontinuation from selumetinib**		**Section**
Visit Description	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5 & beyond (additional visits every 3 weeks)**	**Selumetinib Discontinuation Visit**	**Final follow up 28 days post last dose of selumetinib**	
Day	**-28 to –1**	**1**	**8**	**15**	**22/1**	**43/1**	**64/1**	**85/1**	**N/A**	**N/A**	
Week	**-4 to 0**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**N/A**	**N/A**	
Visit Window (compared to Day 1)	**N/A**	**N/A**	**±2 days**	**±2 days**	**±2 days**	**±1 wk**	**±1 wk**	**±1 wk**	**N/A**	**±7 days (compared to treatment disc visit)**	
ECG	X	X							X		6.3.4
WHO performance status	X	(X)			X	X	X	X	X		6.3.2
Tumour evaluation	X					X		X			6.9.1
Physical examination	X	(X)			X	X	X	X	X		6.3.2
Ophthalmologic examination	X									(X)	6.3.8
Optional tumour biopsy (tissue) at disease progression									X		6.7.3
Dispense selumetinib		X			X	X	X	X			5.1.1
Selumetinib dosing		Continuous bd dosing →									5.1.3
Gemcitabine dosing		X	X		Gemcitabine on Day 1 & 8 of each cycle →						5.1.3
Cisplatin dosing		X			X	X	X	X			5.1.3
Check returned study medication					X	X	X	X	X		5.1.10

The SRC may decide to investigate alternative chemotherapy schedules with continuous selumetinib dosing e.g. gemcitabine with fractionated cisplatin chemotherapy (Days 1 and 8) or gemcitabine with carboplatin, pemetrexed with cisplation, pemetrexed with fractionated cisplatin (Days 1 and 8) or pemetrexed with carboplatin. In these cases the schedule of assessments will be as detailed in Table 3 except for the PK assessments and study treatment dosing, which will conducted as per Table 4.

Table 4 Study Plan – PK & Study treatment dosing – Continuous Selumetinib Dosing (alternative chemotherapy dosing schedules)

	Visit		1	2	3	4	5	6	7	8	Discontinuation from		Section
	Visit Description		Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5 & beyond (additional visits every 3 weeks)	Selumetinib Discontinuation Visit	Final follow up 28 days post last dose of selumetinib	
	Day		-28 to –1	1	8	15	22/1	43/1	64/1	85/1	N/A	N/A	
	Week		-4 to 0	1	2	3	4	7	10	13	N/A	N/A	
Dosing Schedule (for each cycle)	Visit Window (compared to Day 1)		N/A	N/A	±2 days	±2 days	±2 days	±1 wk	±1 wk	±1 wk	N/A	±7 days (compared to treatment disc visit)	
Fractionated cisplatin • Continuous selumetinib bd • Gemcitabine Day 1 & 8 • **Cisplatin Days 1 & 8**	PK plasma sample collection	Selumetinib			X								6 5 1
		Gemcitabine			X								6 5 1
		Cisplatin			X								6 5 1
	Study treatment dosing	Selumetinib		Continuous bd dosing →									5 1 3
		Gemcitabine		X	X		Gemcitabine infusion on Day 1 & 8 in each cycle →						5 1 3
		Cisplatin		X	X		Cisplatin infusion on Day 1 & 8 in each cycle →						5 1 3
Replace cisplatin with carboplatin • Continuous selumetinib	PK plasma sample collection	Selumetinib			X		X						6 5 1
		Gemcitabine			X		X						6 5 1
		Carboplatin					X						6 5 1

Table 4 Study Plan – PK & Study treatment dosing – Continuous Selumetinib Dosing (alternative chemotherapy dosing schedules)

	Visit		1	2	3	4	5	6	7	8	Discontinuation from		Section
	Visit Description		Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5 & beyond (additional visits every 3 weeks)	Selumetinib Discontinuation Visit	Final follow up 28 days post last dose of selumetinib	
	Day		-28 to –1	1	8	15	22/1	43/1	64/1	85/1	N/A	N/A	
	Week		-4 to 0	1	2	3	4	7	10	13	N/A	N/A	
Dosing Schedule (for each cycle)	**Visit Window (compared to Day 1)**		N/A	N/A	±2 days	±2 days	±2 days	±1 wk	±1 wk	±1 wk	N/A	±7 days (compared to treatment disc visit)	
	Study treatment dosing	Selumetinib		Continuous bd dosing →									5 1 3
		Gemcitabine		X	X		Gemcitabine infusion on Day 1 & 8 in each cycle →						5 1 3
		Carboplatin		X			X	X	X	X			5 1 3
Replace gemcitabine with pemetrexed • Continuous selumetinib bd • **Pemetrexed Day 1** • Cisplatin Day 1	PK plasma sample collection	Selumetinib					X						6 5 1
		Pemetrexed					X						6 5 1
		Cisplatin					X						6 5 1
	Study treatment dosing	Selumetinib		Continuous bd dosing →									5 1 3
		Pemetrexed		X			X	X	X	X			5 1 3
		Cisplatin		X			X	X	X	X			5 1 3
Fractionated cisplatin and	PK plasma	Selumetinib			X		X						6 5 1
		Pemetrexed					X						6 5 1

Table 4 Study Plan – PK & Study treatment dosing – Continuous Selumetinib Dosing (alternative chemotherapy dosing schedules)

	Visit		1	2	3	4	5	6	7	8	Discontinuation from		Section
	Visit Description		Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5 & beyond (additional visits every 3 weeks)	Selumetinib Discontinuation Visit	Final follow up 28 days post last dose of selumetinib	
	Day		-28 to –1	1	8	15	22/1	43/1	64/1	85/1	N/A	N/A	
	Week		-4 to 0	1	2	3	4	7	10	13	N/A	N/A	
Dosing Schedule (for each cycle)	**Visit Window (compared to Day 1)**		N/A	N/A	±2 days	±2 days	±2 days	±1 wk	±1 wk	±1 wk	N/A	±7 days (compared to treatment disc visit)	
		Cisplatin			X		X						6 5 1
	Study treatment dosing	Selumetinib		Continuous bd dosing →									5 1 3
		Pemetrexed		X			X	X	X	X			5 1 3
		Cisplatin		X	X		Cisplatin infusion on Day 1 & 8 in each cycle →						5 1 3
Replace gemcitabine with pemetrexed and replace cisplatin with carboplatin • Continuous selumetinib bd • **Pemetrexed Day 1** • **Carboplatin Day 1**	PK plasma sample collection	Selumetinib					X						6 5 1
		Pemetrexed					X						6 5 1
		Carboplatin					X						6 5 1
	Study treatment dosing	Selumetinib		Continuous bd dosing →									5 1 3
		Pemetrexed		X			X	X	X	X			5 1 3
		Carboplatin		X			X	X	X	X			5 1 3

The SRC may also investigate an intermittent selumetinib dosing schedule (Days 2 - 19) with various chemotherapy schedules e.g. gemcitabine (Days 1 & 8) with cisplatin (Day 1), gemcitabine with fractionated cisplatin (Days 1 and 8) or gemcitabine with carboplatin, pemetrexed with cisplatin, pemetrexed with fractionated cisplatin (Days 1 and 8) or pemetrexed with carboplatin. In these cases the schedule of assessments will be as detailed in Table 5.

Table 5 Study Plan – Intermittent Selumetinib Dosing

Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**Discontinuation from selumetinib**		**Section**
Visit Description	**Screening**	**Cycle 1**				**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5 & beyond (additional visits every 3 weeks)**	**Selumetinib Discontinuation Visit**	**Final follow up 28 days post last dose of selumetinib**	
Day	**-28 to –1**	**1**	**2**	**8**	**15**	**22/1**	**43/1**	**64/1**	**85/1**	**N/A**	**N/A**	
Week	**-4 to 0**	**1**		**2**	**3**	**4**	**7**	**10**	**13**	**N/A**	**N/A**	
Visit Window (compared to Day 1)	**N/A**	**N/A**		**±2 days**	**±2 days**	**±2 days**	**±1 wk**	**±1 wk**	**±1 wk**	**N/A**	**±7 days (compared to treatment disc visit)**	
Informed consent	X											**4**
Provision of archival tumour material (tissue/cytology), if available (any time during the study)		→										**6.7.1.1**
Screening procedures (incl medical and surgical history, demography, smoking status)	X											**4.3.1** **6.3.1**
Anti-cancer treatment	X										X	**6.3.1** **6.3.11**
Optional genetic consent & sample		X										**6.7.2**
cfDNA Plasma sample		X										**6.7.1.2**
Serum sample for exploratory biomarker analysis		X										**6.7.1.2**

Table 5 Study Plan – Intermittent Selumetinib Dosing

Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**Discontinuation from selumetinib**		**Section**
Visit Description	**Screening**	**Cycle 1**				**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5 & beyond (additional visits every 3 weeks)**	**Selumetinib Discontinuation Visit**	**Final follow up 28 days post last dose of selumetinib**	
Day	**-28 to –1**	**1**	**2**	**8**	**15**	**22/1**	**43/1**	**64/1**	**85/1**	**N/A**	**N/A**	
Week	**-4 to 0**	**1**		**2**	**3**	**4**	**7**	**10**	**13**	**N/A**	**N/A**	
Visit Window (compared to Day 1)	**N/A**	**N/A**		**±2 days**	**±2 days**	**±2 days**	**±1 wk**	**±1 wk**	**±1 wk**	**N/A**	**±7 days (compared to treatment disc visit)**	
Adverse events	X	→										6.4
Concomitant medications	X	→										4.3.1 6.3.11
Vital signs (including height at baseline), weight	X		X	X	X	X	X	X	X	X	X	6.3.3
Concomitant procedures		X	X	X	X	X	X	X	X	X	X	6.3.10
Clinical chemistry/haematology	X		X	X	X	X	X	X	X	X	X	6.3.5
Urinalysis	X											6.3.5
Pregnancy test (pre-menopausal females only)	X	(X)	as clinically indicated →									6.3.6
Plasma sample collection for selumetinib PK				X								6.5.1
Plasma sample collection for gemcitabine PK				X								6.5.1
Plasma sample collection for cisplatin PK (fractionated cisplatin only)				(X)								6.5.1
Echocardiogram/MUGA	X								X		(X)	6.3.7
ECG	X	X	X							X		6.3.4
WHO performance status	X		(X)			X	X	X	X	X		6.3.2

Table 5 Study Plan – Intermittent Selumetinib Dosing

Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**Discontinuation from selumetinib**		**Section**
Visit Description	**Screening**	**Cycle 1**				**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5 & beyond (additional visits every 3 weeks)**	**Selumetinib Discontinuation Visit**	**Final follow up 28 days post last dose of selumetinib**	
Day	**-28 to –1**	**1**	**2**	**8**	**15**	**22/1**	**43/1**	**64/1**	**85/1**	**N/A**	**N/A**	
Week	**-4 to 0**	**1**		**2**	**3**	**4**	**7**	**10**	**13**	**N/A**	**N/A**	
Visit Window (compared to Day 1)	**N/A**	**N/A**		**±2 days**	**±2 days**	**±2 days**	**±1 wk**	**±1 wk**	**±1 wk**	**N/A**	**±7 days (compared to treatment disc visit)**	
Tumour evaluation	X						X		X			**6.9.1**
Physical examination	X		(X)			X	X	X	X	X		**6.3.2**
Ophthalmologic examination	X										(X)	**6.3.8**
Optional tumour biopsy (tissue) at disease progression										X		**6.7.3**
Dispense selumetinib			X			X	X	X	X			**5.1.1**
Selumetinib dosing			bd dosing Days 2 – 19 in each cycle →									**5.1.3**
Gemcitabine dosing		X		X		Gemcitabine on Days 1 & 8 in each cycle →						**5.1.3**
Cisplatin dosing options: - Cisplatin		X				X	X	X	X			**5.1.3**
Fractionated Cisplatin		X		X		Cisplatin Days 1 & 8 in each cycle →						
Carboplatin dosing		X				X	X	X	X			
Pemetrexed dosing		X				X	X	X	X			**5.1.3**
Check returned study medication						X	X	X	X	X		**5.1.10**

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.

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 E of this Clinical Study Protocol.

6.3 Safety procedures

6.3.1 Enrolment and screening

At enrolment, each potential patient will provide informed consent prior to starting any study specific procedures (see sections 6.7.1.1 and 6.7.2 and Appendix D 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, 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.

Where available for a patient, the local *KRAS* testing results will be collected.

Each patient will undergo screening (see Table 3, Table 4 & Table 5) during the 28 days prior to admission to confirm eligibility (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 complete physical examination will be performed at screening, prior to the first dose of selumetinib in cycle 1 (if screening assessment was greater than 14 days before first dose of selumetinib), at the beginning of each cycle thereafter and at discontinuation.

Performance status will be assessed at screening, prior to the first dose of selumetinib in cycle 1 (if screening assessment was greater than 14 days before first dose of selumetinib), at the

beginning of each cycle thereafter and at discontinuation according to WHO criteria as follows:

0 - Fully active, able to carry out all pre-disease activities without restrictions

1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light housework, office work

2 - Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 - Completely disabled, cannot carry on self-care, totally confined to bed or chair

6.3.3 Vital signs

Pulse rate and blood pressure

Supine resting blood pressure and pulse rate will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size after 10 minutes rest. Assessments will be performed as follows:

- Screening
- First selumetinib dosing day Cycle 1; pre-dose, 1.5 and 6 hours post dose
- Cycle 1 Day 8
- Cycle 1 Day 15
- First selumetinib dosing day of each subsequent Cycle
- Discontinuation visit
- Final follow up visit

Body temperature

Body temperature will be measured in degrees Celsius at the following visits:

- Screening
- Pre-dose first selumetinib dosing day Cycle 1
- Cycle 1 Day 8

- Cycle 1 Day 15
- First selumetinib dosing day of each subsequent Cycle
- Discontinuation visit
- Final follow up visit

Weight

Weight will be performed at screening, pre-dose on first selumetinib dosing day Cycle 1, on Day 1 of each Cycle, at the discontinuation visit and at the final follow up visit.

Height

Height will be assessed at screening only.

Additional vital sign measurements may be recorded at the discretion of the Investigator if clinically indicated, e.g. for additional temperature assessments for patients with AEs of low neutrophil count.

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

6.3.4 ECG

ECGs will be analysed locally. Patients should be supine and at rest 10 minutes prior to recording the ECG(s). After paper ECG(s) have been recorded, the Investigator or designated physician will review each of the ECG(s) and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. Parameters including heart rate, duration of QRS complex, RR, PR and QT intervals will be collected. QTcF will be calculated by AstraZeneca from the data provided.

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.

Screening ECG

At screening all patients will have a single 12-lead ECG performed. The screening ECG can be conducted up to 28 days prior to Cycle 1 Day 1.

Treatment Phase ECGs

Patients will have 12-lead ECGs captured in triplicate (5 mins apart) pre-dose, 1.5 and 6 hours post-dose on first Day of selumetinib dosing in Cycle 1.

Patients on intermittent selumetinib dosing (Days 2-19) should have a single 12-lead ECG assessment taken on Cycle 1 Day 1 before chemotherapy administration.

Single ECGs should also be performed at the time of significant LVEF drop (refer to Section 6.3.7) and on occurrence of any cardio respiratory adverse event with no obvious diagnosis. For patients with new or worsening respiratory symptoms (such as dyspnoea, cough), an ECG is recommended and additionally at the discretion of the Investigator if clinically indicated. Adverse events should be managed in accordance with local clinical practice. For guidance on specific adverse events management please refer to the separate study aid "Guidance for Management of Specific Adverse Events in Studies of Selumetinib".

A single 12-lead ECG is also required at discontinuation of treatment.

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the visits as indicated in the Study Plan (see Table 3 & Table 5). In order to prepare chemotherapy prescriptions, clinical chemistry and haematology samples may be taken up to 3 days before the visit date. On days when samples for selumetinib PK are taken, the safety samples should be taken before the first dose of selumetinib. The following laboratory variables will be measured:

Clinical chemistry

Serum (S)/Plasma (P)-Albumin

S/P-ALT

S/P-AST

S/P-Alkaline phosphatase

S/P-Bilirubin, total

S/P-Calcium, total

S/P-CK-MB*

S/P-Creatinine

S/P-Magnesium

S/P-Phosphate

S/P-Potassium

S/P-Sodium

S/P-total protein

S/P-Troponin*

S/P-Urea nitrogen

Haematology

Blood (B)-Haemoglobin

B-Leukocyte

B-Absolute leukocyte differential count:

- Neutrophils
- Lymphocytes
- Monocytes
- Basophils
- Eosinophils

B-Platelet count

Urinalysis**

U-Glucose

U-Protein

U-Blood

S – serum P - plasma B – blood U - urine

* Troponin (isoform as per institution norm) should be assessed at screening, on occurrence of significant LVEF drop or cardiorespiratory events with no obvious cause. Additionally, CK-MB to be performed in case of cardio respiratory events with no obvious cause if this is the institution's normal clinical practice.

** Urinalysis will be performed at screening. Additional urinalysis assessments will be performed if clinically indicated. Urine microscopy to be performed if other urinalysis measurements are abnormal/if clinically indicated.

NB. In case a subject shows an AST or ALT ≥ 3xULN or total bilirubin ≥ 2xULN please refer to Appendix G 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law' for further instructions.

Clinical chemistry and haematology testing will be repeated as clinically indicated as part of the routine management of the patient on the occurrence of AEs.

All patients with an AST, ALT or bilirubin value ≥ 1.5 x ULN at time of the last dose of selumetinib should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 28 days (±7days) after permanent discontinuation of selumetinib.

For blood volume see Section 6.8.1.

6.3.6 Pregnancy test

A pregnancy test will be performed at screening, prior to starting treatment (not required if performed within 14 days of starting treatment) and as clinically indicated during study treatment for female pre-menopausal patients. Investigator should at each visit assess the patient's compliance to contraceptive measures and perform a test if required.

6.3.7 Echocardiogram or MUGA

An echocardiogram will be conducted at screening and 12 weekly intervals while on treatment. A further echocardiogram should be performed as part of the assessment package for any cardio respiratory adverse event with no obvious diagnosis (obvious causes will be managed in accordance with local clinical practice) and additionally at the discretion of the Investigator if clinically indicated.

LVEF, end diastolic and end systolic left ventricular volumes should be recorded at each echocardiogram assessment. Patients experiencing an asymptomatic but clinically significant drop in LVEF ≥ 10% and absolute value < 55% should be managed according to the algorithm provided as a separate study aid in the "Guidance for Management of Specific Adverse Events in Studies of Selumetinib". Patients who have a drop of LVEF ≥ 10 percentage points and to an absolute value < 55% from baseline prior to discontinuation of selumetinib should, where possible, have a follow-up echocardiogram performed 28 days after permanent discontinuation of selumetinib in order to document reversibility.

If an echocardiogram scan cannot be taken a MUGA scan to assess LVEF will be conducted.

The modality of the cardiac function assessments must be consistent within patient, i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans. The patient should also be examined using the same machine and operator throughout the study wherever possible.

Important cardiac symptoms should be reported as AEs/serious adverse events (SAEs) accordingly. Congestive cardiac failure should be treated and followed according to standard medical practice.

6.3.8 Ophthalmologic examination

An ophthalmologic examination (best corrected visual acuity, intraocular pressure, slit lamp fundoscopy) should be performed at screening and if a patient experiences any visual symptoms (including blurring of vision). Examinations should be the same as screening with additional tests if clinically indicated e.g. fundus photography if abnormality detected and consider OCT scans. Patients who have a retinal abnormality prior to discontinuation of selumetinib should, if practicable, have a follow up eye examination performed 28 days after discontinuation of selumetinib in order to document reversibility.

6.3.9 Troponin and CK-MB

Troponin (isoform as per institution norm) should be assessed at screening, on occurrence of significant LVEF drop or cardiorespiratory events with no obvious cause. Additionally, CK-MB is to be performed in case of cardio-respiratory events with no obvious cause if this is the institution's normal clinical practice.

6.3.10 Concomitant procedures

All concomitant procedures e.g. surgery, should be collected from Cycle 1 Day 1 until termination of the study.

6.3.11 Follow-up

A post study assessment will be performed at the time selumetinib is permanently discontinued (see Study Plan Table 3, Table 4 & Table 5).

In addition, patients should be followed up for 28 days (+/-7 days) days after the last dose of selumetinib for any new reports of adverse events. Patients should also be asked about concomitant medications, including any anti-cancer treatments, at this follow-up.

6.4 Adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are 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 following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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 (see disease progression).

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 is an AE occurring during any study phase (i.e. run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions
- Is 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 B 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 +/-7 days after selumetinib is discontinued. SAEs occurring in the follow-up period should be reported to AstraZeneca in the usual manner (see Section 6.4.4).

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s) 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 selumetinib the Investigator should notify AstraZeneca.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade/changes in CTCAE grade according to the National Cancer Institute (NCI) CTCAE Version 4
- Whether the AE is serious or not
- Causality due to selumetinib ("yes" or "no")
- Causality due to chemotherapy [named] ("yes" or "no")
- Causality due to study procedure ("yes" or "no")
- Action taken with regard to selumetinib
- Action taken with regard to chemotherapy [named]
- Whether event constitutes an SAE
- Outcome
- Treatments in relation to event

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

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

- Causality assessment in relation to other medication
- Causality assessment in relation to chemotherapy [named]
- Causality assessment in relation to selumetinib
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. 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.

After study completion (i.e. after any scheduled follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. However, 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 selumetinib, the Investigator should notify AstraZeneca, Patient Safety department.

The grading scales found in the current National Cancer Institute (NCI) 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. The version used in this study is NCI CTCAE Version 4. A copy of the current CTCAE version can be downloaded from the Cancer Therapy Evaluation Program 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?’

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 B of this Clinical Study Protocol.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient 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 eCRF. 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 (e.g. 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.

NB. Cases where a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix G 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

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.

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 eCRF module, but should not be reported as a SAE during the study

- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes

- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes

6.4.4 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 eCRF.

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 5.4 of the IB for selumetinib.

6.5 Pharmacokinetics

6.5.1 Collection of pharmacokinetic samples

In the continuous selumetinib dosing with gemcitabine (Day 1 & 8) & cisplatin (Day 1) chemotherapy schedule, the following samples will be taken:

Venous blood samples (2ml) for determination of concentrations of selumetinib and N-desmethyl selumetinib in plasma will be taken, pre-dose and at 0.5, 1, 1.5, 2, 4, 8 and 10 hours post dose on Cycle 1 Day 8 & Cycle 2 Day 1. Other metabolites (e.g. selumetinib amide) may also be determined.

Venous blood samples (2ml) will be collected for the determination of gemcitabine and it's metabolite Deoxy-1,1-Difuorouridine (dFdU) in plasma at the following timepoints: predose, midway through the infusion (i.e. at 15 minutes after the start of a 30 minute infusion), at the end of the infusion and at 0.5, 1, 1.5, 3.5, 7.5 and 9.5 hours after the end of the infusion on Cycle 1 Day 8 and Cycle 2 Day 1.

Venous blood samples (6ml) for determination of concentrations of cisplatin (total and/or unbound platinum) in plasma will be taken, pre-dose, midway through the infusion (i.e. at 1 hour after the start of a 2 hour infusion), end of infusion and at 0.5, 1, 2, 3.5, 5.5 and 7.5 hours after the end of the infusion on Cycle 2 Day 1.

Table 6 Pharmacokinetic schedule – continuous selumetinib dosing with gemcitabine (Day 1 & 8) & cisplatin (Day 1) chemotherapy schedule

	Time for blood samples	**Visit**
Selumetinib and N-desmethyl selumetinib	Pre-dose, 0.5, 1, 1.5, 2, 4, 8 and 10 hours post dose	Cycle 1 Day 8 Cycle 2 Day 1
Gemcitabine & dFdU	Predose, midway through the infusion (i.e. at 15 minutes after the start of a 30 minute infusion), end of the infusion, 0.5, 1, 1.5, 3.5, 7.5 and 9.5 hours after the end of the infusion	Cycle 1 Day 8 Cycle 2 Day 1
Cisplatin (total &/or unbound platinum)	Pre-dose, midway through the infusion (i.e. at 1 hour after the start of a 2 hour infusion), end of infusion and at 0.5, 1, 2, 3.5, 5.5 and 7.5 hours after the end of the infusion	Cycle 2 Day 1

The dates and times of collection of each sample will be recorded.

On PK dosing days, the second dose of selumetinib should be taken after the last PK sample has been taken on that day.

The total number of samples and the total volume of blood taken from each patient will not exceed that presented in Table 8.

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

The SRC may investigate alternative dosing schedules. Examples of the different schedules and PK sampling requirements are recorded in Table 7. On PK sample days the sampling timepoints will remain the same as detailed in Table 6.

If cisplatin is replaced by carboplatin on a continuous selumetinib dosing schedule, venous blood samples (6mL) for determination of concentrations of carboplatin (total and/or unbound platinum) in plasma will be taken, pre-dose, midway through the infusion (i.e. at 30 minutes after the start of a 1 hour infusion), end of infusion and at 0.5, 1, 1.5, 3.5 and 5.5 hours after the end of the infusion on Cycle 2 Day 1.

(Note: PK samples for carboplatin will not be taken if on an intermittent selumetinib dosing schedule)

If gemcitabine is replaced by pemetrexed on a continuous selumetinib dosing schedule, venous blood samples (2ml) for determination of concentrations of pemetrexed in plasma will be taken, pre-dose, end of infusion and at 0.5, 1.5, 3, 4, 6 and 8 hours after the end of infusion on Cycle 2 Day 1.

(Note: PK samples for pemetrexed will not be taken if on an intermittent selumetinib dosing schedule)

Table 7 Pharmacokinetic sampling for alternative dosing schedules

Dose Schedule	Visit	PK Sampling
Continuous Selumetinib Gemcitabine Days 1 & 8 Cisplatin Days 1 & 8	Cycle 1 Day 8	Selumetinib and N-desmethyl selumetinib Gemcitabine & dFdU Cisplatin (total &/or unbound platinum)
Continuous Selumetinib Gemcitabine Days 1 & 8 Carboplatin Day 1	Cycle 1 Day 8	Selumetinib and N-desmethyl selumetinib Gemcitabine & dFdU

Table 7 Pharmacokinetic sampling for alternative dosing schedules

Dose Schedule	Visit	PK Sampling
	Cycle 2 Day 1	Selumetinib and N-desmethyl selumetinib Gemcitabine & dFdU Carboplatin (total &/or unbound platinum)
Continuous Selumetinib Pemetrexed Day 1 Cisplatin Day 1	Cycle 2 Day 1	Selumetinib and N-desmethyl selumetinib Pemetrexed Cisplatin (total &/or unbound platinum)
Continuous Selumetinib Pemetrexed Day 1 Cisplatin Days 1 & 8	Cycle 1 Day 8	Selumetinib and N-desmethyl selumetinib Cisplatin (total &/or unbound platinum)
	Cycle 2 Day 1	Selumetinib and N-desmethyl selumetinib Pemetrexed Cisplatin (total &/or unbound platinum)
Selumetinib Days 2-19 Gemcitabine Days 1 & 8 Cisplatin Day 1	Cycle 1 Day 8	Selumetinib and N-desmethyl selumetinib Gemcitabine & dFdU
Selumetinib Days 2-19 Gemcitabine Days 1 & 8 Cisplatin Days 1 & 8	Cycle 1 Day 8	Selumetinib and N-desmethyl selumetinib Gemcitabine & dFdU Cisplatin (total &/or unbound platinum)
Selumetinib Days 2-19 Gemcitabine Days 1 & 8 Carboplatin Day 1	Cycle 1 Day 8	Selumetinib and N-desmethyl selumetinib Gemcitabine & dFdU
Selumetinib Days 2-19 Pemetrexed Day 1 Cisplatin Day 1	No PK sampling required	
Selumetinib Days 2-19 Pemetrexed Day 1 Cisplatin Days 1 & 8	Cycle 1 Day 8	Selumetinib and N-desmethyl selumetinib Cisplatin (total &/or unbound platinum)
Selumetinib Days 2-19 Pemetrexed Day 1 Carboplatin Day 1	No PK sampling required	

6.5.2 Determination of drug concentration in pharmacokinetic samples

Samples for determination of selumetinib and its metabolites and gemcitabine and its metabolite and cisplatin (total and/or unbound platinum) concentrations in plasma will be analysed by Laboratories on behalf of the Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

If cisplatin is replaced by carboplatin and administered with selumetinib and gemcitabine (or pemetrexed if applicable) then the samples for the determination of carboplatin (total and/or unbound platinum) concentrations in plasma will be analysed by Laboratories on behalf of the Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

If gemcitabine is replaced by pemetrexed and administered with selumetinib and cisplatin or carboplatin then the samples for determination of pemetrexed concentrations in plasma will be analysed by Laboratories on behalf of the Clinical Bioanalysis Alliance, AstraZeneca R&D, 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. selumetinib, N-desmethyl selumetinib, gemcitabine, dFdU, pemetrexed, cisplatin [total and/or unbound platinum] or carboplatin [total and/or unbound platinum]) at the time of receipt by the bioanalytical laboratory will be analysed.

In addition, the selumetinib 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 CSR.

6.6 Pharmacodynamics

Not applicable.

6.7 Exploratory research

6.7.1 Exploratory biomarker research

Biological samples (i.e. plasma, serum, archived tumour samples) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity (i.e. possible identification of predictive biomarker/s), 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 CSR.

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.

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

6.7.1.1 Collection of archival tumour samples

As part of the main consent, all patients will be asked to provide consent to supply an archival tumour sample, if a sample taken at the time of diagnosis (or a more recent tumour sample collected prior to study entry) is available.

Samples will preferably be a tumour sample, supplied as a formalin fixed paraffin embedded block (tissue derived from the primary or 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, presented on glass slides may be provided. If only a cytology sample is available, this can be provided in a cell block, cytospin or cell smear format. Samples provided will primarily be used to assess *KRAS* mutation status; however, further analysis may be performed in the future (such as but not limited to relevant tumour mutations, RNA [gene expression profiling], protein expression [by immunohistochemistry etc.]).

6.7.1.2 Collection of exploratory blood-borne biomarkers

Exploratory biomarker research samples

A mandatory blood sample (10ml) will be taken to provide one sample of serum on Cycle 1 Day 1 (pre-dose). The samples will be analysed for a range of oncology biomarkers which may correlate with drug response.

Collection of plasma for exploratory analysis of cfDNA

All patients will be required to provide a 10 ml blood sample for plasma on Cycle 1 Day 1 (pre-dose). These samples will be used for the extraction and analysis of circulating free DNA (cfDNA). The cfDNA will be used for the analysis of *KRAS* mutation status, but may also be used for the determination of the mutation status of other tumour related genes.

This area of mutation analysis is exploratory and it is hoped that such analyses will aid the development of methodologies for analysis of tumour mutation status. It is hoped that this will lessen the burden for providing tumour biopsy samples for analysis in the future. Data generated from this analysis will not be used to aid patient recruitment in this study.

6.7.2 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 CSR.

6.7.2.1 Collection of pharmacogenetic samples

A 10ml blood sample for genetic research will be obtained from the patients immediately prior to dosing. 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 genetic analysis. If for any reason the sample is not drawn prior to dosing it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

6.7.3 Collection of optional disease progression tumour biopsy

Once objective disease progression occurs while on study treatment an optional tumour biopsy may be collected (if consent obtained) between the time of disease progression and the end of the follow-up period (28+/-7 days after selumetinib is discontinued). This will enable a comparison to be made of (for example) tumour genetics and relevant signal transduction pathways between the archival and disease progression tumour biopsies, and also the evolution of the tumour biology in response to treatment with selumetinib can be explored. Such changes may reflect an evolution in phenotype of the tumour, which ultimately may guide future treatment decisions post progression on selumetinib.

Samples will preferably be a tumour sample, supplied as a formalin fixed paraffin embedded block. If this is not possible, 10-20 slides of freshly prepared unstained 5 micron sections from the disease progression tumour block, presented on glass slides may be provided.

Optional tumour biopsies should only be collected for those patients who have provided an archival tumour sample (i.e. a tissue sample not a cytology sample) at baseline and preferably a pharmacogenetic blood sample.

Patients who provide consent to the optional tumour biopsy, and discontinue study treatment for other reasons than objective tumour progression, e.g. due to toxicity reasons, will not have a discontinuation biopsy taken.

6.8 Biological sampling procedures

6.8.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study from screening up to the end of Cycle 2 is shown in Table 8. The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on selumetinib become available. However, the total volume will not exceed 250 ml over a two month period.

Table 8 Volume of blood to be drawn from each patient during first two cycles of treatment

		Sample volume (ml)	Number of samples	Total volume (ml)
Safety	Clinical chemistry	10	5	50
	Haematology	4	5	20

Table 8 Volume of blood to be drawn from each patient during first two cycles of treatment

		Sample volume (ml)	Number of samples	Total volume (ml)
Pharmacokinetics	Selumetinib and gemcitabine or pemetrexed	2	34	68
Pharmacokinetics	Cisplatin or carboplatin	6	9	54
CfDNA (plasma)		10	1	10
Exploratory biomarker (serum)		10	1	10
Pharmacogenetics		10	1	10
TOTAL*				222

* The above volume of blood is based on the scheduled assessments for the continuous selumetinib dosing schedule with gemcitabine (Days 1 & 8) and cisplatin (Day 1). Other dosing schedules may be employed but require lower total volumes.

6.8.2 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.

Biological samples for future research will be retained at AstraZeneca or it's designee for a maximum of 25 years from the date of the last patient's last visit, after which they will be destroyed. The results from future analysis will not be reported in the CSR but will be reported separately in the bioanalytical method validation report.

6.8.2.1 Pharmacokinetic samples

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

Any PK sample remaining after analysis for selumetinib and its metabolites may be used for biomarker analyses. These analyses are for AstraZeneca use only and will not be included in the CSR.

6.8.2.2 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 data may be correlated with clinical data, samples destroyed in the case of withdrawal of consent and regulatory audit enabled.

Residual material may be retained for the analysis of other biomarkers. These analyses are for AstraZeneca use only and will not be included in the CSR.

6.8.2.3 Samples for pharmacogenetic research

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

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. DNA is a finite resource that be be used up during analyses. Samples will/may be stored and used until no further analyses are possible or the maximum storage time has been reached.

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 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.

6.8.3 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 C 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.

All archival tumour samples should be shipped at ambient temperature as per the Laboratory Manual to the AstraZeneca designated central Contract Research Organisation.

6.8.4 Chain of custody of biological samples

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

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

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

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

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

6.8.5 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.

As collection of these biological samples is a voluntary part of the study then the patient may continue 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.

6.9 Anti-tumour activity

6.9.1 Tumour assessments

RECIST 1.1 guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumour response criteria are presented in Appendix F of this Clinical Study Protocol.

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. The methods of assessment of tumour burden used at baseline, CT/MRI of chest and abdomen (including liver and adrenal glands), must be used at each subsequent follow-up assessment. Additional imaging may be performed to evaluate additional anatomical locations that may be involved based on signs and symptoms of individual patients. Follow-up assessments should be performed every 6 weeks (± 1 week) after the start of treatment until the patient has been on treatment for 6 months and then every 12 weeks (± 1 week) until discontinuation of selumetinib or withdrawal of consent. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits whilst the patient remains on study treatment.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 guidelines for response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease).

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated.

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 NTLs is usually not sufficient to qualify for unequivocal disease progression status.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plans in Section 6.1 and Appendix F, Section 4.1.

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)
- Selumetinib pharmacokinetics (Secondary)
- Gemcitabine pharmacokinetics (Secondary)
- Cisplatin pharmacokinetics (Secondary)
- Carboplatin pharmacokinetics (if applicable) (Secondary)
- Pemetrexed pharmacokinetics (if applicable) (Secondary)
- Tumour response (Secondary)
- Metabolite pharmacokinetics (secondary)
- Exploratory biomarkers (serum) (Exploratory)
- Pharmacogenetics (Exploratory)

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

7.2 Determination of sample size

The primary objective of this study is to investigate the safety, tolerability and RP2D of selumetinib when administered in combination with selected chemotherapies. Hence the number of patients has been based on the desire to obtain adequate tolerability, safety and pharmacokinetic data while exposing as few patients as possible to the investigational product and procedures.

For the combination dose finding phase of the study, cohorts of 3-6 evaluable patients will be required. The total number of patients will depend upon the number of doses investigated in this phase.

Following the completion of Part A, the SRC may decide to commence with a Part B. Approximately 12 additional evaluable patients will be recruited at the RP2D from Part A and/or lower dose levels, in order to explore further the safety and tolerability of a chemotherapy regimen at these doses. Multiple expansion phases may run in parallel.

7.3 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, ECG changes, physical examinations, echocardiogram/MUGA and ophthalmologic examinations. These will be collected for all patients. Appropriate summaries of these data will be presented as described in Section 7.9.

ECG Changes

QTc will be calculated using both Bazett's and Fridericia's formulae.

Creatinine Clearance

Estimated creatinine clearance will be calculated using the Cockcroft and Gault formula (Appendix H).

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 and reported as such in the CSR. 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 concentration data for selumetinib, N-desmethyl selumetinib, gemcitabine, dFdU, pemetrexed, cisplatin (total and/or unbound platinum) and carboplatin (total and/or unbound platinum) (if applicable) will be performed by Clinical Pharmacology and Pharmacometrics, AstraZeneca.

Pharmacokinetic parameters in plasma will be derived using standard non-compartmental methods using actual elapsed time from dosing.

If data permits and unless otherwise stated, the following PK parameters will be determined for selumetinib, N-desmethyl selumetinib, gemcitabine, dFdU, pemetrexed, cisplatin (total and/or unbound platinum) and carboplatin (total and/or unbound platinum) (if applicable):

C_{max} Maximum plasma concentration ($C_{max,}$ ng/mL), obtained directly from the observed concentration versus time data.

t_{max} Time to C_{max} ($t_{max,}$ h)

AUC	Area under the plasma concentration-time curve from zero to infinity (AUC, ng*h/mL), calculated by linear up/log down trapezoidal summation.
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration [$AUC_{(0-t)}$, ng*h/mL], calculated by linear up/log down trapezoidal summation.
CL/F	Apparent oral plasma clearance (CL/F, L/h selumetinib only).
CL	Plasma clearance (CL, L/h gemcitabine, dFdU, pemetrexed, total and unbound platinum in cisplatin and carboplatin)
V_{ss}/F	Apparent volume at distribution equilibrium, MRT*CL/F (V_{ss}/F, L, selumetinib only)
V_{ss}	Volume of distribution MRT*CL (V_{ss}, L, gemcitabine, dFdU, pemetrexed, total and unbound platinum in cisplatin and carboplatin)
$t_{1/2}$	Terminal half-life ($t_{1/2}$, h)
λ_z	Terminal rate constant (λ_z, L/h)

Metabolite (N-desmethyl selumetinib) to parent drug ratios will be calculated for the primary PK parameters AUC and $C_{max.}$

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression to determine t1/2 (t1/2, interval)
- Number of data points (t1/2, N) included in the log-linear regression analysis to determine λz. A minimum of 3 data points will be used for λz determination
- Coefficient of determination for calculation of λz (Rsq). The λz and related parameters will be reported only if Rsq is 0.800 or more
- Percentage of AUC obtained by extrapolation (%AUCex); if the extrapolated area (%AUCex) is greater than 20% then AUC for that specific profile will not be reported

7.5 Calculation or derivation of pharmacodynamic variables

Not applicable

7.6 Calculation or derivation of exploratory research variables

Analysis of cfDNA - cfDNA will be extracted from the plasma sample for analysis of tumour specific mutations. This will be undertaken using standard genetic analysis techniques.

Any residual plasma or plasma derived DNA will be utilised for future exploratory biomarker research into factors that may influence development of cancer and/or response to selumetinib (and/or agents used as comparators or as combinations).

Further biomarker research analysis - Serum sample will be collected for future exploratory biomarker research into factors that may influence development of cancer and/or response to selumetinib (and/or agents used as comparators or as combinations). Methods of analysis may include investigation of genetic variability, gene expression profiling, protein expression profiling.

Results from the exploratory biomarker and pharmacogenetic research will be reported separately from the CSR for the main study.

7.7 Calculation or derivation of tumour response variables

At each visit patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD depending on the status of their disease compared to baseline and previous assessments.

Progression of TLs 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.

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

ORR is defined as the percentage of patients who have at least one confirmed visit response of CR or PR prior to any evidence of progression (as defined by RECIST 1.1).

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.

In the case of best overall response (BOR) of stable disease, measurements should have met the stable disease criteria at least once after the study start and at least 6 weeks (±1 week) from the date of the first dose.

When the Investigator is in doubt as to whether progression of disease has occurred and therefore reassesses the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

BOR will be calculated as the best response recorded for each patient from the date study treatment started until data cut off.

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.

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

7.8 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 9.

Table 9 Analysis sets

Analysis Set	Definition
Safety	All patients who received at least 1 dose of selumetinib
Pharmacokinetics	An adequate PK profile will be a profile where the majority (at least 80%) of the PK samples have been collected and a sample has been collected around the C_{max} (for selumetinib) or at the end of infusion (chemotherapy)
Tumour response	Dosed patients with a baseline tumour assessment.

Table 9 Analysis sets

Analysis Set	Definition
Exploratory biomarkers	All patients that participate in the exploratory biomarker research

7.9 Methods of statistical analysis

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

Data from the dose finding phase (Part A) and the dose expansion phase (Part B) will be presented separately.

Demographic data

Characteristics of the patients, including medical history and disease characteristics at baseline will be listed for each patient and summarised by dose group, study part and cohort.

Reasons for discontinuation of investigational product will be listed including the study day of treatment discontinuation and will be summarised by dose group, study part and cohort.

Exposure

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

Total exposure and total time on study (date of last dose minus date of first dose) will be summarised by the following: mean, standard deviation, minimum, maximum, median and number of observations. The number and percentage of patients with at least one selumetinib dose interruption and at least one selumetinib dose reduction will be presented. In addition, the number and percentage of patients with at least one chemotherapy dose delay and at least one chemotherapy dose reduction will be presented.

Safety

Safety data will not be formally analysed. All patients who receive at least one dose of selumetinib will be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

Data from all cycles of initial treatment will be combined in the presentation of safety data. AEs will 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 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 but will not be included in the 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, echocardiogram/MUGA data, ophthalmologic examination data, 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

Plasma concentrations of selumetinib, N-desmethyl selumetinib, gemcitabine, dFdU, pemetrexed, cisplatin (total and/or unbound platinum) and carboplatin (total and/or unbound platinum) (if applicable) will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by dose group.

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
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for AUC, $AUC_{(0-t)}$, and C_{max}:

- 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
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for CL/F, CL, V_{ss}/F, V_{ss} and $t_{½\lambda z}$:

- Arithmetic mean
- Standard deviation
- Minimum
- Maximum
- Number of observation
- The following summary statistics will be presented for tmax:
- Median

- Minimum
- Maximum
- Number of observations

The pharmacokinetic data for selumetinib, N-desmethyl selumetinib, gemcitabine, dFdU, pemetrexed, cisplatin (total and/or unbound platinum) and carboplatin (total and/or unbound platinum) (if appropriate) 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.

Exploratory biomarker research and pharmacogenetics

The number of patients that will agree to participate in the exploratory biomarker and genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated.

The data from the exploratory research and pharmacogenetics are not intended to be reported in the CSR.

Tumour response

Tumour response data will be summarised for dosed patients with measurable disease at baseline.

Tumour response data will be listed and summarised by dose using the following response categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and Non-Evaluable (NE).

Waterfall plots (bar charts) indicating the percentage change from baseline in sum of the diameters of TLs at week 6 and best change will be produced by dose level.

BOR and ORR will be summarised by study part and cohort.

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 Team Leader at the AstraZeneca Research and Development site recorded below.

Name	Role in the study	Address & telephone number
	Study Team Physician responsible for the protocol at central R&D site	
	Study Team Leader responsible for the protocol at central R&D site	
	24-hour emergency cover at central R&D site.	

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 eCRF and on the overdose eCRF module.

An overdose with no associated symptoms is only reported on the overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs during 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.

Treatment of chemotherapy overdoses should be as per the specific chemotherapy & the local practices.

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.

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 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 within 1 or 5 days for SAEs, (see Section 6.4.4) and within 28 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.3.2 Paternal exposure

Pregnancy of a patient's partner is not considered to be an adverse event. However, any conception occurring from the date of dosing until 12 weeks after dosing should be reported to AstraZeneca and followed up for its outcome (including spontaneous miscarriage, elective termination, normal birth or congenital abnormality).

The outcomes of any conception must be documented in the "Pregnancy Outcome Report" form.

Male patients must refrain from fathering a child during the study and 12 weeks (see Section 4.3) following the last dose of the last study treatment (or longer if required for the combination chemotherapy agents), since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated.

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Clinical Study Protocol Appendix B	
Drug Substance	Selumetinib (AZD6244; ARRY-142886
Study Code	D1532C00070
Edition Number	1
Date	

Appendix B
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.

Clinical Study Protocol Appendix C

Drug Substance	Selumetinib (AZD6244; ARRY-142886)
Study Code	D1532C00070
Edition Number	1
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Appendix C
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 **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** 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 **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).**
- **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.

Clinical Study Protocol Appendix D

Drug Substance	Selumetinib (AZD6244; ARRY-142886)
Study Code	D1532C00070
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Appendix D
Ethical and Regulatory Requirements

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1. ETHICAL AND REGULATORY REQUIREMENTS

1.1 Ethical conduct of the study

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

1.2 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 will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

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

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 with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

1.3 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
- 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.

1.4 Changes to the protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of each 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 1.2.

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.

1.5 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.

Clinical Study Protocol Appendix E

Drug Substance	Selumetinib (AZD6244; ARRY-142886)
Study Code	D1532C00070
Edition Number	1
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Appendix E
Data and Study Management

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1. DATA AND STUDY MANAGEMENT

1.1 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.

1.2 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

1.3 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).

1.4 Source data

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

1.5 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.

1.6 Data management by AstraZeneca or delegate

Data management will be performed by

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

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. External data where appropriate (e.g. pk) will 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.

1.7 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 the optional 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.

1.7.1 Archiving of study documents

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

1.8 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 Selumetinib.

AstraZeneca

Clinical Study Protocol Appendix F	
Drug Substance	Selumetinib (AZD6244; ARRY-142886)
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Appendix F
Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours)

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LIST OF TABLES

1. INTRODUCTION

This appendix details the implementation of RECIST (Response Evaluation Criteria in Solid Tumours) 1.1 guidelines (Eisenhauer et al 2009)for the study with regards to investigator assessment of tumour burden including protocol-specific requirements for this study.

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

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

Measurable lesions

A lesion, not previously irradiated, that can be measured accurately at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have a short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline. Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs)

- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by CT or MRI

- Previously irradiated lesions as localised post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTLs at baseline and followed up as part of the NTL assessment

- Skin lesions assessed by clinical examination

- Brain metastasis

Special cases

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

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

Target lesions

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

Non-target lesions

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

3. METHODS OF MEASUREMENT

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

The methods to be used for RECIST assessment are summarised in Table 1 and those excluded for tumour assessments in this study are discussed below, with the rationale provided.

Table 1 Summary of Methods of Assessment

Target Lesions	Non target lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Plain X-ray (includes chest X-ray)	Plain X-ray (includes chest X-ray)
	Clinical examination	Clinical examination
		Ultrasound
		Bone scan
		FDG-PET

3.1 CT and MRI

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

In this study it is recommended that CT examinations will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contrast media administration

is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For assessment of brain lesions MRI is the preferred method.

3.2 Clinical examination

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are then assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in patients that also have other lesions assessable by CT, MRI or plain Xray and to identify the presence of new lesions.

3.3 X-rays

3.3.1 Plain X-ray

Plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

3.3.2 Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

3.4 Ultrasound

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

3.5 Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

3.6 Tumour markers

Not applicable.

3.7 Cytology and histology

Histology will not be used as part of the tumour response assessment per RECIST 1.1.

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

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

3.8 Isotopic bone scan

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

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

3.9 FDG-PET scan

FDG-PET (fluorodeoxyglucose positron emission tomography) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. The methods of assessment of tumour burden used at baseline, CT/MRI of chest and abdomen (including liver and adrenal glands), must be used at each subsequent follow-up assessment. Additional imaging may be performed to evaluate additional anatomical locations that may be involved based on signs and symptoms of individual patients. Follow-up assessments should be performed every 6 weeks (± 1 week) after the start of treatment until the patient has been on treatment for 6 months and then every 12 weeks (± 1 week) until discontinuation of study treatment or withdrawal of consent. Any other sites at which new disease is suspected should also be adequately imaged at follow-up. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits whilst the patient remains on study treatment.

4.2 Target lesions

4.2.1 Documentation of target lesions

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

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

Special cases:

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

4.2.2 Evaluation of target lesions

Table 2 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 2 Overall Visit Response for Target Lesions

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

4.3 Non-Target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator. Table 3 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 3 Overall Visit Response for Non-Target Lesions

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

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

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

4.4 New Lesions

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

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

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

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

4.5 Symptomatic deterioration

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

Patients with 'symptomatic deterioration' requiring discontinuation of study treatment without objective evidence of disease progression at that time will undergo no further tumour assessments in this study. Tumour response data for such patients will be censored at the date of their last RECIST assessment.

4.6 Evaluation of Overall Visit Response and Best Overall Response

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

Table 4 Overall Visit Response

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
IR = incomplete response, NE = not evaluable, NA = not applicable (relevant when no NTLs at baseline)

5. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardised protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

5.1 CT Scan

CT scans of the chest and abdomen (including liver and adrenal glands) should be contiguous throughout all the anatomical regions of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

Anatomic coverage

Optimal anatomic coverage for lung cancer is the chest and abdomen (including liver and adrenal glands). Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

Intravenous contrast administration

Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvic MRI with contrast. If MRI cannot be performed then CT without intravenous contrast is an option for the thorax, abdomen and pelvic examinations. For assessment of brain lesions MRI is the preferred method.

Slice thickness and reconstruction material

It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for the measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TLs should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not “selected” images of the apparent lesion.

5.2 MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and

pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

5.3 FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

5.3.1 PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

6. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 45 (2009) 228-247.

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Clinical Study Protocol Appendix G	
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Appendix G
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

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1. INTRODUCTION

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

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

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

2. DEFINITIONS

Potential Hy's Law (PHL)

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.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

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

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

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

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study 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

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

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

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

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

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

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

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

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

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

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

determine whether HL criteria are met. Update the SAE report according to the outcome of the review

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

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

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

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

7. 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 6?

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

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

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

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

8. REFERENCES

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

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

Clinical Study Protocol Appendix H	
Drug Substance	Selumetinib (AZD6244; ARRY-142886)
Study Code	D1532C00070
Edition Number	1
Date	

Appendix H
Cockcroft-Gault Formula

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1. COCKCROFT-GAULT FORMULA

The Cockcroft-Gault formula has been provided for reference, as the protocol allows for the serum creatinine clearance to be calculated using the Cockcroft-Gault formula (see Section 4.2, Exclusion criteria):

For serum creatinine values in μmol /L:

Estimated creatinine clearance rate (eC_{Cr}) (for men) = [(140 – age) x weight (kg) x 1.23] / creatinine (μmol/L)

eC_{Cr} (for women) = [(140 – age) x weight (kg) x 1.04] / creatinine (μmol/L)

For serum creatinine values in mg/dL:

eC_{Cr} (for men) = [140 – age] x weight (kg) / [72 x creatinine (mg/dL)]

eC_{Cr} (for women) = 0.85 x ([140 – age] x weight (kg) / [72 x creatinine (mg/dL)])

Ref: Cockcroft D, Gault MD. Nephron 16: 31-41, 1976.

AstraZeneca

Clinical Study Protocol Appendix I	
Drug Substance	Selumetinib (AZD6244; ARRY-142886)
Study Code	D1532C00070
Edition Number	1
Date	

Appendix I
Heart Classifications (NYHA and Canadian Grading of Angina)

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1. NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF HEART DISEASE

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

2. CANADIAN CARDIOVASCULAR SOCIETY GRADING OF ANGINA PECTORIS

Grade	Description
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

3. REFERENCES

New York Heart Association 1994
The Criteria Committee of the New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th edition. Boston, MA: Little, Brown & Co; 1994:253-256.

Campeau Lucien. Grading of angina pectoris
Circulation 1976;54:5223 Available on the Canadian Cardiovascular Society Website at www.ccs.ca