AstraZeneca

Revised Clinical Study Protocol

Drug Substance	Selumetinib (AZD6244; ARRY-142886)
Study Code	D1532C00079
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Date	

A Phase III, Double-Blind, Randomised, Placebo-Controlled Study to Assess the Efficacy and Safety of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Combination with Docetaxel, in Patients receiving second line treatment for *KRAS* Mutation-Positive Locally Advanced or Metastatic Non Small Cell Lung Cancer (Stage IIIB – IV) (SELECT-1)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1			
2			
3			

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

PROTOCOL SYNOPSIS

A Phase III, Double-Blind, Randomised, Placebo-Controlled Study to Assess the Efficacy and Safety of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Combination with Docetaxel, in Patients receiving second line treatment for *KRAS* Mutation-Positive Locally Advanced or Metastatic Non Small Cell Lung Cancer (Stage IIIB – IV) (SELECT-1)

International Co-ordinating Investigator

Study centre(s) and number of patients planned

Approximately 500 *KRAS* mutation-positive patients receiving second line treatment for locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) will be recruited from approximately 220 centres globally. In order to randomise approximately 500 patients it is expected that an estimated 3332 patients will be enrolled (assuming a 15% randomisation rate for NSCLC patients who are *KRAS* mutation positive and fulfill the patient selection criteria as detailed in Section 4).

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2013	III
Estimated date of last patient completed	Q1 2017	

Objectives

Primary objective

1. To assess the efficacy in terms of Progression Free Survival (PFS) of selumetinib in combination with docetaxel compared to placebo in combination with docetaxel.

Secondary objectives

1. To assess the efficacy of selumetinib in combination with docetaxel, compared with placebo in combination with docetaxel in terms of:

   – Overall Survival (OS)

- Objective Response Rate (ORR)
- Duration of Response (DoR)

2. To assess the efficacy of selumetinib in combination with docetaxel compared to placebo in combination with docetaxel on NSCLC symptoms

3. To assess the safety and tolerability profile of selumetinib in combination with docetaxel compared with placebo in combination with docetaxel

4. To investigate the pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered in combination with docetaxel (other selumetinib metabolites e.g. selumetinib amide, may also be assessed).

Exploratory objectives

1. To describe the impact of treatment and disease state on symptom distress and interference with activity levels as measured by the LCSS, and health related quality of life (HRQoL) as measured by the 36 Item Short-Form Health Survey Version 2 (SF-36v2)

2. To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, AEs and/or safety parameters if deemed appropriate

3. To investigate the use of circulating free tumour DNA (cfDNA) derived from plasma, for the analysis of *KRAS* mutation status at screening and treatment discontinuation

4. To explore the influence of *KRAS* mutation subtypes on response to treatment

5. 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)

6. To explore potential biomarkers in residual biological samples (e.g. tumour and/or plasma) which may influence development of cancer (and associated clinical characteristics) and/or response.

7. To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility.

Study design

This is a phase III, double-blind, randomised, placebo-controlled study assessing the efficacy and safety of selumetinib (75 mg, orally uninterrupted twice daily [bd]) in combination with docetaxel (intravenously [iv] 75 mg/m^2, on day 1 of every 21 day cycle) in patients receiving

ment for *KRAS* mutation-positive locally advanced or metastatic NSCLC (Stage IIIB – IV).

Patients will be selected on the basis of the *KRAS* mutation status of their tumour sample; patients whose tumour sample is positive for *KRAS* mutation and fulfil all eligibility criteria will be randomised in a ratio of 1:1 to receive:

- Selumetinib 75 mg bd in combination with docetaxel 75 mg/m^2

Or

- Placebo in combination with docetaxel 75 mg/m^2.

Patients will be stratified at randomisation based on their WHO Performance Status (1/0) and tumour histology (squamous/non-squamous).

The *KRAS* mutation status of the patient's tumour must be determined by the designated central laboratory using the cobas® *KRAS* Mutation Test
submitted under the Investigational Device Exemption (IDE) in the US

Following randomisation, patients will attend for visits on Day 8, 15, 22, 43 and every 3 weeks thereafter for as long as they are receiving study treatment. Tumour evaluation according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) guidelines will be performed at screening, week 6, week 12 and every 6 weeks thereafter, relative to the date of randomisation. Patients must be followed until evidence of RECIST 1.1-defined progression (regardless of reason for treatment discontinuation). It is important that patients are assessed according to the intended scanning schedule to prevent the bias in analysis that can occur if one treatment group is assessed more often or sooner than the other. All imaging assessments including unscheduled visit scans should be collected on an ongoing basis and sent to an AstraZeneca (AZ) appointed Clinical Research Organisation (CRO) to enable central analyses if required.

If a patient discontinues study treatment (selumetinib/placebo and docetaxel) for reasons other than objective disease progression, RECIST 1.1 assessments should continue according to the original schedule until objective disease progression. RECIST 1.1 measurements will be used to derive the primary variable of PFS and secondary variables of ORR and DoR.

Once a patient has had objective disease progression recorded and discontinued all study treatment, they are to be followed up for survival status every 8 weeks until death, withdrawal of consent or the end of the study. LCSS and SF-36v2 assessments are to be completed before any study related assessment as per study plan. Assessments should be performed until objective disease progression with an additional assessment 30 days following objective disease progression.

If a patient wishes to withdraw their consent to further participation in the study, including survival follow-up (which could be conducted by telephone) this should be clearly documented in the patient notes and in the clinical study database.

Target patient population

Male and female patients aged 18 years and over with centrally confirmed *KRAS* mutation-positive locally advanced or metastatic NSCLC who are eligible for second-line treatment and have had no prior treatment with docetaxel or a MEK inhibitor. Patients must have measurable disease (using Computer Tomography [CT]/Magnetic Resonance Imaging [MRI]) as defined by RECIST 1.1 guidelines, confirmation of histological or cytological locally advanced or metastatic NSCLC and WHO Performance Status of 0-1.

Investigational product, dosage and mode of administration

Selumetinib, as the Hyd-sulfate, will be administered orally as three 25mg blue capsules twice a day (total dose of 75mg twice a day), in combination with docetaxel 75 mg/m^2 iv given on Day 1 of each 21 day cycle.

Comparator, dosage and mode of administration

Three placebo capsules will be administered orally uninterrupted bd, in combination with docetaxel 75 mg/m^2 iv, administered on Day 1 of each 21 day cycle.

G-CSF administration

All patients will receive pegylated Granulocyte Colony Stimulating Factor (G-CSF) at a minimum of 24 hours after the administration of every docetaxel dose and not within 14 days prior to the next docetaxel administration.

Duration of treatment

Treatment with selumetinib or matching placebo will commence following randomisation and continue until objective disease progression, intolerable toxicity or the occurrence of another discontinuation criterion.

Docetaxel treatment will be administered iv and patients are expected to receive up to 6 cycles of treatment administered on day 1 of every 21 day cycle until objective disease progression, intolerable toxicity or the occurrence of another discontinuation criterion. Further cycles of docetaxel may be administered if the treating investigator feels it is beneficial and it does not contravene local practice. Investigators may decide to reduce the number of cycles of docetaxel if significant toxicity develops. If docetaxel is discontinued for reasons other than disease progression, selumetinib (or matching placebo) should be continued until disease progression, intolerable toxicity or the occurrence of another discontinuation criterion.

Patients will be permitted to continue to receive study treatment (docetaxel, selumetinib or placebo), after objective disease progression if, in the opinion of the investigator, they are continuing to derive clinical benefit, in the absence of significant toxicity and it does not contravene local practice, after consultation with AZ. Such patients will attend visits every 3

weeks and have the same on-study assessments performed excluding RECIST1.1 scans until discontinuation of the last study treatment.

Outcome variable(s):

Primary Outcome variable:

- PFS using investigator site assessments according to RECIST 1.1

Secondary Outcome variables:

- OS
- ORR using investigator site assessments according to RECIST 1.1
- DoR using investigator site assessments according to RECIST 1.1
- Time to symptom progression as measured by the Average Symptom Burden Index (ASBI) score of the Lung Cancer Symptom Scale (LCSS)
- Symptom improvement rate as measured by the ASBI score of the LCSS

Safety:

- Adverse events
- Clinical chemistry, haematology and urinalysis
- Vital signs
- ECHO/MUGA
- Ophthalmological examination

Pharmacokinetic:

- Where sample collection and PK analysis allow, output from mixed effect modelling for selumetinib and N-desmethyl selumetinib will be produced which may include, but not be restricted to, Cmax and AUC (other selumetinib metabolites e.g. selumetinib amide, may also be assessed)

Exploratory Outcome variables:

- Individual items of the LCSS: Symptom distress and interference with activity levels
- SF-36v2 domain scale scores and physical and mental component summary scores

t from both graphical and/or appropriate PK/PD modelling techniques

- *KRAS* mutation status of plasma derived DNA from samples collected at screening and treatment discontinuation
- *KRAS* mutation subtype(s)
- Host genetic polymorphisms
- Biomarkers to response or development of cancer

Statistical methods

Two treatment groups will be randomised (1:1) into the study:

- Selumetinib 75 mg bd in combination with docetaxel (iv 75 mg/m2 on day 1 of every 21 day cycle)

Or

- Placebo in combination with docetaxel (iv 75 mg/m2 on day 1 of every 21 day cycle)

Therefore, for efficacy there will be one treatment comparison of interest:

- Selumetinib 75mg bd in combination with docetaxel 75mg/m^2 vs placebo in combination with docetaxel 75mg/m^2

PFS is the primary endpoint. However, the study has been sized to characterise the OS benefit of selumetinib 75mg bd in combination with docetaxel. Approximately 500 *KRAS* mutation positive tumour patients will be randomised between the two treatment arms to obtain approximately 325 death events (65% maturity). The final analysis of PFS will take place on a pre-specified date when it is predicted that 325 death events will have occurred. The exact date will be predicted by modelling the blinded death rate data.

If the true OS hazard ratio (HR) for the comparison of selumetinib 75mg bd in combination with docetaxel 75mg/m^2 vs placebo in combination with docetaxel 75mg/m^2 is 0.72, this number of events will provide at least 80% power to demonstrate a statistically significant difference for OS, assuming a 2% 1-sided Type I error. This OS HR corresponds to an approximate 2-month improvement in median OS over an estimate of 5.2 months (estimated from D1532C00016) for placebo in combination with docetaxel, assuming proportional hazards and exponential data distribution. A 2-month improvement in median OS is regarded as clinically meaningful. The smallest treatment difference that would be statistically significant at the final analysis is an OS HR of approximately 0.80 (0.796 if exactly 325 OS events).

Efficacy data will be analysed on an intention-to-treat basis using randomised treatment. PFS, OS and time to symptom progression using the ASBI will be analysed using a stratified log-rank test. The results will be presented in terms of the HR, associated two-sided confidence interval (CI) and p-value. Kaplan-Meier (KM) plots of PFS, OS and time to symptom progression will also be presented. ORR and symptom improvement rate using the ASBI will be analysed using a logistic regression adjusted for the stratification factors WHO Performance Status (1/0) and tumour histology (squamous/non-squamous).

In order to describe the nature of the benefits of selumetinib treatment, PFS, OS, ORR, time to symptom progression and symptom improvement rate will be tested at a 2-sided significance level of 5%. However, in order to strongly control the type I error at 2.5% 1-sided, a multiple testing procedure (MTP) with an alpha-exhaustive recycling strategy (Burman et al 2009) will also be employed across the primary endpoint (PFS) and key secondary endpoints (i.e. OS and ORR).

Safety data will be summarised and listed for all patients who received at least one dose of study treatment (selumetinib/placebo) based on treatment received. No formal statistical testing will be performed on the safety data. Adverse events will be summarised by preferred term and system organ class (using the Medical Dictionary for Regulatory Activities [MedDRA]). Summaries of AEs by causality and CTC grade will also be presented.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALK	Anaplastic lymphoma kinase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASBI	Average Symptom Burden Index (of the Lung Cancer Symptom Scale)
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area under plasma concentration / time curve
AZ	AstraZeneca
bd	Twice daily
BICR	Blinded Independent Central Review
BP	Blood pressure
BRAF	v-raf murine sarcoma viral oncogene homolog B1
cfDNA	Circulating free tumour deoxyribonucleic acid
CK-MB	Creatine Kinase-MB
CI	Confidence Interval
Cmax	Maximum plasma concentration
CPK	Creatine phosphokinase
CR	Complete response
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DCO	Data cut off
DLT	Dose limiting toxicity

Abbreviation or special term	Explanation
DNA	Deoxyribonucleic acid
DoR	Duration of Response
DUS	Disease under Study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EDR	Early Discrepancy Rate
EGFR	Epidermal growth factor receptor
ERK	Extracellular signal-regulated kinase
EU	European Union
FFPE	Formalin fixed paraffin embedded
FSH	Follicle Stimulating Hormone
FSI	First Subject In
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
γGT	Gamma glutamyl transferase
GMP	Good Medical Practice
HR	Hazard Ratio
HIV	Human immunodeficiency virus (HIV)
HRQoL	Health-Related Quality of Life
IATA	International Air Transport Association
IB	Investigator Brochure
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IDE	Investigational Device Exemption
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intention to Treat

Abbreviation or special term	Explanation
iv	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
KRAS mutation positive	Mutations in *KRAS* have been detected
KRAS Wild type / mutation negative	Mutations in *KRAS* have not been detected
LCS	Lung Cancer Subscale
LCSS	Lung Cancer Symptom Scale
LDR	Late Discrepancy Rate
LH	Luteinizing Hormone
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LSLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
MCS	Mental Component Summary
MEK	Mitogen-Activated protein Kinase
MTP	Multiple Testing Procedure
MRI	Magnetic resonance imaging
MUGA	Multi Gated Acquisition Scan
Mutations in *KRAS* have been detected	Mutations in *KRAS* have been detected in codon 12, 13 or 61
Mutations in *KRAS* have not been detected	Mutations in *KRAS* have not been detected in codon 12, 13 or 61
NSCLC	Non-Small Cell Lung Cancer
NTL	Non-target Lesion
NYHA	New York Heart Association
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
OCT	Optical Coherence Tomography
od	Once daily
ORR	Objective Response Rate
OS	Overall Survival

Abbreviation or special term	Explanation
P	Probability
PCS	Physical Component Summary
PD	Pharmacodynamic
PFS	Progression Free Survival
PGx	Pharmacogenetic Research
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial Response
PRO	Patient-Reported Outcome
PTEN	Phosphatase and tensin homolog
QTcF	QT corrected using Fridericia's formula
RAS	Reticular activating system
RAS/RAF/MEK/ERK	Intracellular pathway frequently mutated in cancers
RECIST 1.1	Response Evaluation Criteria in Solid Tumours version 1.1
RPSFT	Rank Preserving Structural Failure Time
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	Statistical Analysis Plan
SF-36v2	36 Item Short-Form Health Survey Version 2
SD	Stable Disease
SPC	Summary of Product Characteristics
TL	Target Lesion
TSP	Time to Symptom Progression
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBDC	Web Based Data Capture
WHO	World Health Organisation

1. INTRODUCTION

1.1 Background

1.1.1 Non-Small Cell Lung Cancer (NSCLC)

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total) (GLOBOCAN 2008). NSCLC represents approximately 80% to 85% of all lung cancers). Unfortunately, at the time of diagnosis approximately 70% of NSCLC patients already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of early stage NSCLC patients who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters & Le Chevalier 2005). While there are usually no signs or symptoms in the early stages of lung cancer, as the disease progresses common symptoms include coughing up blood and persistent cough, weight loss, breathlessness, tiredness/fatigue and chest or shoulder pain (Kris et al 2003). As the disease progresses these symptoms, and typical lung cancer therapies can have a considerable impact on patients' HRQoL (Akin et al, 2010; Belani et al, 2006).

A number of molecular abnormalities have been shown to be characteristic of certain lung cancers. The point mutations of the *KRAS* gene are identified in approximately 10 to 30% of advanced NSCLC, mainly in adenocarcinomas (Eberhard et al 2005). Most frequently somatic RAS mutations affect codons 12, 13 and 61 resulting in accumulation of active RAS protein in the cell and subsequent activation of signalling pathways involved in malignant transformation (Baselga & Rosen 2008). *KRAS* mutation has been documented as being a prognostic factor, with patients with a *KRAS* mutation-positive tumour having a worse prognosis (Mascaux et al 2005). More recently, further studies on correlations of mutation status with response have indicated that *KRAS* mutation status is associated with resistance to therapy with epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (Massarelli et al 2007, Miller et al 2008, Pao et al 2005) and erlotinib combined with chemotherapy (Eberhard et al 2005).

Despite advances in diagnosis, imaging, staging and treatment, the estimated overall five-year survival for patients with NSCLC in Europe continues to be low, 11% (D'Addario et al 2010). Once patients experience treatment failure following initial therapy, the outlook for patients with refractory advanced NSCLC is extremely poor, with response to further systemic treatment approximately 10% (Hanna et al 2004) and median survival of approximately 6 months. Thus, the goal for therapy for such patients is to prolong survival without substantial negative impacts on HRQoL (Belani et al, 2006).

First-line chemotherapy for advanced/metastatic NSCLC usually comprises 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. Docetaxel and pemetrexed are standard chemotherapies recommended for use in second-line NSCLC (Peters et al 2012).

1.1.2 Mitogen activated protein kinase (MEK)

The intracellular Ras regulated *RAF/MEK/ERK* protein kinase signal cascade is a key pathway involved in cellular proliferation and there is a strong link between deregulation of this pathway and uncontrolled cell proliferation and survival (Chow et al 2005).

Activation of *RAF/MEK/ERK* signalling pathway is implicated in various cancers, including NSCLC (Khushalani & Adjei 2006).

It is anticipated that inhibition of *MEK* activity should inhibit transduction of the mitogenic and survival signals via *RAF/MEK/ERK* regardless of the nature of the upstream activation, resulting in an inhibition on tumour proliferation, differentiation and survival.

1.1.3 Selumetinib

Selumetinib (AZD6244; ARRY 142886) is a potent, selective, uncompetitive inhibitor of MEK, licensed for development by AstraZeneca Pharmaceuticals from Array BioPharma. Array BioPharma was responsible for the first-into-human study; the remainder of the clinical development programme for oncology indications is the responsibility of AstraZeneca.

1.1.4 Pre-clinical experience with selumetinib

The scientific hypothesis for selumetinib is based on inhibition of the RAF/*MEK/ERK* kinase cascade that when activated plays a pivotal role in cell proliferation and survival and is considered a key pathway for therapeutic intervention in oncology. *The RAF/MEK/ERK* kinase cascade is activated by *Raf* binding to activated *RAS* which itself can be activated either by cell surface receptors, e.g. receptor tyrosine kinases or by mutation *RAS* itself. *RAF/MEK/ERK* signaling can also be activated in cancer by mutation activation of *BRAF* such as occurs in cutaneous melanoma. Mutated *KRAS* is constitutively activated compared to wild-type *KRAS* by virtue of reduced GTPase activity which enables the GTP-bound form of *KRAS* to recruit the effector *Raf* proteins which then activate the *MEK/ERK* kinase pathway. Therefore it is considered that tumors carrying a *KRAS* mutation will activate *MEK-ERK* signaling and be more dependent upon this pathway for sustaining the oncogenic phenotype.

Selumetinib has been studied in various pre-clinical models, including studies of both monotherapy and combination therapy in NSCLC and *KRAS* mutated cancer models. For example in vivo studies in *KRAS* mutation positive human cancer xenografts have demonstrated the potential to improve the therapeutic efficacy of selumetinib in combination with cytotoxic drugs including docetaxel. In vitro studies support the hypothesis that dependence upon *MEK-ERK* signaling is more likely in cells in which mutational activation of the pathway is observed as a consequence of *BRAF* or *RAS* gene mutation.

Pre-clinical evidence supporting the evaluation of selumetinib in *RAS* mutated cancers

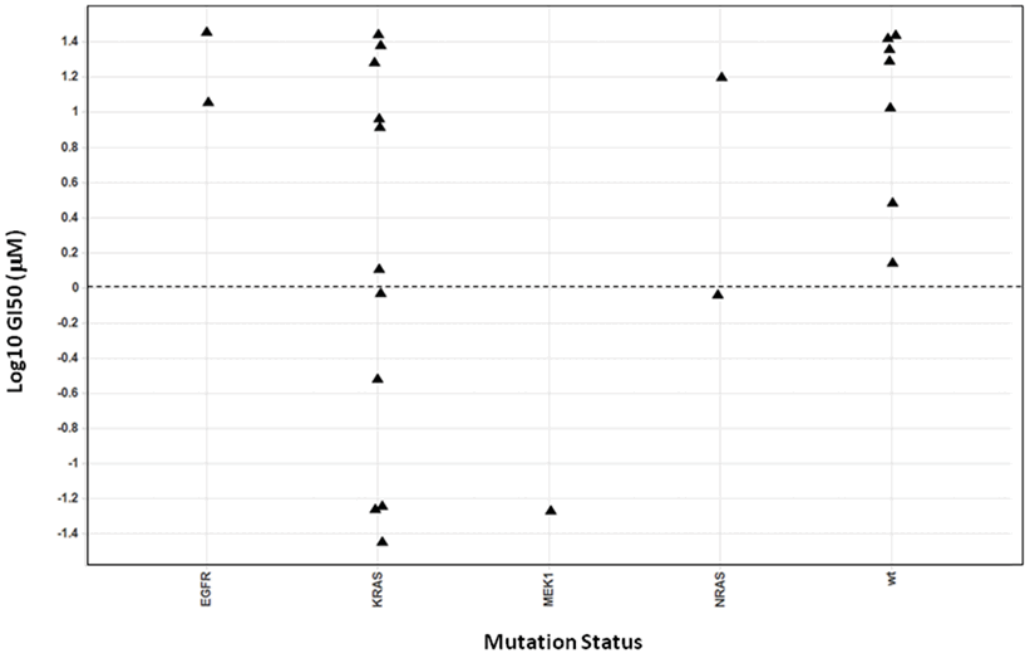
***In Vitro* Data**

To determine the effects of selumetinib on cell viability, a panel of human tumor cell lines was exposed to varying concentrations of selumetinib. The GI50 values ranged from <10 nM to >10 μM and most of the cell lines that were sensitive to selumetinib contained either a

BRAF or *RAS* gene mutation (Dry et al 2010). Sensitive cell lines included those derived from colorectal, NSCLC, pancreatic and melanoma tumors. This data is supported by studies by collaborators and has been observed for other MEK inhibitors. As a test for selecting cells that are growth inhibited by selumetinib, a *BRAF/RAS* test has a sensitivity of 0.86 and specificity of 0.76 (Dry et al 2010).

Data shown in Figure 1 from an AstraZeneca NSCLC cell panel indicates that the cell lines with a growth inhibitory response to MEK inhibition (sensitive classified as GI50 < 1 µM, dotted line in Figure 1) 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 *MEK* inhibiton monotherapy *in vitro*.

Figure 1 Growth inhibitory responses to MEK inhibition



Published literature also supports the notion that the most *MEK* inhibitor sensitive cell lines tend to carry *BRAF* or *RAS* gene mutation, however this is not an exclusive relationship and cell lines without known *MEK/ERK* pathway associated mutations can show sensitivity to *MEK* inhibition (Jing et al 2012; Garon et al 2010; Meng et al 2010).

In Vivo Data

Selumetinib has been tested in 3 human lung tumor xenografts carrying a *KRAS* mutation (Table 1). In one of these, Calu-6, selumetinib achieves complete growth inhibition whilst the other two models are only moderately sensitive with treatment causing 40 to 50% tumor growth inhibition. Selumetinib has also been tested in a primary explant model of NSCLC in which neither *KRAS* nor *EGFR* is mutated – the response to selumetinib monotherapy is classed as moderately sensitive.

Table 1 Selumetinib in NSCLC tumour xenografts

Model	Tumor growth inhibition
Calu-6 – mutKRAS, sensitive *in vitro*	100 % at 25 mg/kg bd 60% at 3 mg/kg bd
A549 – mutKRAS, mutLKB1, resistant *in vitro*	53% at 25 mg/kg qd
NCI-H460 – mutKRAS, mutPI3KCa, mutLKB1, resistant *in vitro*	43% at 25 mg/kg bd
NCI-H1975 – mutEGFR(L858R/T790M), resistant *in vitro*	46% at 25 mg/kg bd*
NCI-H2122 – mutKRAS, mutLKB1	32.6% at 50 mg/kg qd
L004F5 – wild-type (primary explants, not cell line derived)	50% at 25 mg/kg qd
Collaborative study (Takahashi et al 2012)	
NCI-H441 (orthotopic model) – mutKRAS, insensitive *in vitro*	71%[a] at 12.5 mg/kg bd 82%[a] at 25 mg/kg bd
NCI-H460 (orthotopic model) –mutKRAS, insensitive *in vitro*	65%[a] at 12.5 mg/kg bd 90%[a] at 25 mg/kg bd

bd=twice daily; qd=once daily.
[a] Measurements of primary lung tumor volume.
* Not statistically significant compared to control

Overall, these pre-clinical data demonstrate that the majority of cell lines that are sensitive to the growth inhibitory effects of selumetinib are those that carry an activating mutation in the pathway. In NSCLC this effectively amounts to the presence of a *KRAS* mutation since the incidences of *MEK1*, *BRAF*, and *NRAS* mutations are rare in comparison (Marks et al 2008). For *in vivo* data, the coverage of *KRAS* wild type NSCLC models is limited to a single primary explant model so it is not known if the response in *in vivo* models is conditioned by *KRAS* mutation to the same extent as observed *in vitro*.

Preclinical evidence to support the combination of selumetinib with docetaxel

***In Vitro* Data**

The potential for selumetinib to sensitize cells to the effects of docetaxel in the absence of any effect of selumetinib alone has been tested in a small panel of NSCLC cell lines insensitive to the growth inhibitory effects of selumetinib exposed to varying doses of docetaxel and a fixed dose of selumetinib. In all cases, selumetinib treatment did not significantly alter the responses to docetaxel suggesting that in *in vitro* assays, selumetinib does not act as a true sensitizer to docetaxel, regardless of the cell's response to MEK inhibition.

***In Vivo* Data**

Selumetinib has been combined with docetaxel using human xenograft tumor models (Table 2, Holt et al 2012), showing the combination to be more effective than the respective monotherapies. The NCI-H1975 model that carries an activating and gatekeeper mutation in EGFR shows no benefit of the Selumetinib/taxotere combination over taxotere alone.

Table 2 In vivo combination effects of Selumetinib

Xenograft Model	Treatment[a]	Result (% tumor growth inhibition, compared to control)
SW620 human colorectal cancer xenograft	Control	-
	Selumetinib 25 mg/kg bd	74
	Taxotere 15 mg/kg (once weekly)	12
	Selumetinib + taxotere	98
HCT-116 human colorectal cancer xenograft	Control	-
	Selumetinib 25 mg/kg bd	64.9
	Taxotere 15 mg/kg (once weekly)	93.4
	Selumetinib + taxotere	123.2
A549 human non-small cell lung cancer xenograft	Control	-
	Selumetinib 25 mg/kg od	50
	Taxotere 15 mg/kg (once weekly)	5.8
	Selumetinib + taxotere	74.8
L004 Kras/EGFR wild type lung cancer patient derived NSCLC xenograft mouse model	Control	-
	Selumetinib 25 mg/kg od	40
	Taxotere 15 mg/kg (once weekly)	>100
	Selumetinib + taxotere	>100
NCI-H1975 human non-small cell lung cancer xenograft (mutant EGFR L858R/T790M)	Control	-
	Selumetinib 25 mg/kg bd	46 *
	Taxotere 15 mg/kg (once weekly)	114
	Selumetinib + taxotere	114

[a] Selumetinib and taxotere were administered according to their usual monotherapy schedules.
bd = twice daily; od = once daily. * not statistically significant compared to control.

A study recently published describes a murine 'co-clinical' trial in which mice genetically engineered to develop NSCLC driven by *KRAS* mutation were treated with either docetaxel or the combination of docetaxel plus selumetinib (Chen et al 2012). These studies confirmed findings in cell line derived xenografts, that the addition of selumetinib to docetaxel can result in significantly enhanced tumor regression in mut*KRAS* NSCLC.

Overall, the pre-clinical evidence is consistent with both the selection of *KRAS* mutation positive NSCLC as a patient group for testing and demonstrating the therapeutic efficacy of selumetinib plus docetaxel.

Further information of pre-clinical experience is presented in the current Investigator Brochure (IB).

1.1.5 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.

Phase I combination study D1532C00004

Study D1532C00004 is a phase I, open-label study to assess the safety, tolerability and PK of selumetinib Hyd-Sulfate in patients with advanced solid tumours when administered in combination with other anti-cancer agents.

The dose escalation part of the study in combination with docetaxel enrolled two selumetinib dose cohorts at 50 mg twice daily (cohort 1) and 75 mg twice daily (cohort 2). No dose limiting toxicities (DLTs) occurred in the 3 patients enrolled in cohort 1, so the selumetinib dose was increased for cohort 2. During the evaluation of cohort 2, it became apparent that treatment practices differed between sites with respect to G-CSF use with docetaxel administration. A differential occurrence of DLTs (haematological) occurred between cohort 2 patients who had not received G-CSF primary prophylaxis (2/2 DLTs) and cohort 2 patients who had received G-CSF primary prophylaxis (0/5 DLTs).

Further information on most common causally-related AEs reported in this study can be found in the IB. Information supporting the prophylactic use of G-CSF with the combination of selumetinib and docetaxel is found in Section 3.2.3 of this protocol.

The preliminary PK data suggest there are no measurable interactions that significantly affect the plasma exposure of either selumetinib or docetaxel.

Phase II combination programme with selumetinib and docetaxel in patients with NSCLC

Study D1532C00016

This study was designed to test the following hypotheses:

- That inhibition of MEK may provide clinical benefit in patients with activation of the MAPK pathway resultant from a mutation of *KRAS*

- That inhibition of MEK may prevent cancer cell survival following chemotherapy induced damage

Selumetinib 75 mg bd was investigated in combination with docetaxel 75 mg/m^2 every 21 days in a Phase II randomised, double blind, placebo-controlled study which enrolled 87 patients with *KRAS* mutation-positive NSCLC who were eligible for second-line treatment with docetaxel (D1532C00016; Janne et al 2012).

The study demonstrated that the addition of selumetinib to docetaxel provided a marked difference in tumour response rate (37% vs 0%, p=0.00001) and PFS (5.3 months vs 2.1 months; HR 0.58; 80% CI 0.42-0.79; 1-sided p=0.0138) and a numerical improvement in median OS from 5.2 months to 9.4 months, (HR 0.80; 80% CI 0.56-1.14; 1-sided p=0.2069). Post hoc analyses of disease-related symptoms based on the Lung Cancer Subscale (LCS), a commonly used endpoint in NSCLC, also showed that significantly more patients treated with the combination of selumetinib and docetaxel experienced clinically important improvements in LCS compared with those who received placebo and docetaxel (LCS improvement rates: 44% versus 25%, Odds Ratio [OR] 2.50, 80% CI 1.34 to 4.77). The time to worsening of LCS was also in favour of the combination. Patients who received selumetinib and docetaxel experienced a higher incidence of grade >3 AEs (81.8% vs 66.7%), SAEs (59.1% vs 31.0%), and hospitalization due to AE (48% vs 19%) than in the placebo in combination with docetaxel group, though there was no increase in mortality due to AEs. The most common AE findings that were more frequently experienced by patients receiving selumetinib in combination with docetaxel were as anticipated based on monotherapy profiles of each agent: low neutrophil count, diarrhoea, infections, nausea, vomiting, peripheral oedema, rash (mainly acneiform) and stomatitis. Patients who received selumetinib in combination with docetaxel also experienced febrile neutropenia more frequently and neutropenia was more severe. There was also a greater amount of low grade “intolerable events” on the experimental arm which compromised selumetinib dosing through dose interruptions.

The data above suggests that the combination of selumetinib and docetaxel induces a high frequency and depth of tumour shrinkage which translates into tumour response as assessed by RECIST methodology and an improvement in PFS when compared to that achieved by docetaxel alone. The tumour shrinkage also translates into a reduction in a patient’s disease related symptom burden. These effects on PFS and tumour shrinkage occurred despite the increased toxicity profile of the combination compared to that of docetaxel alone. A substantial proportion of patients discontinued the combination of selumetinib with docetaxel because of adverse events therefore it may be hypothesised that a greater degree of clinical benefit and in particular a more enduring effect on overall survival may occur with improved tolerability of the combination. This may be achieved by the administration of primary prophylactic G-CSF, use of current toxicity management guidelines and imparting data from other studies within the selumetinib programme that may assist treating physicians make appropriate dose modifications in the event of toxicity.

Study D1532C00064

An ongoing randomised phase II study D1532C00064 (SELECT-2) is comparing the benefit-risk ratio of selumetinib in combination with two doses of docetaxel (60mg/m^2 and 75mg/m^2) compared with placebo in combination with docetaxel (75mg/m^2) as 2nd line therapy for patients with advanced or metastatic NSCLC. The study has a primary endpoint of progression free survival. Initial study design included unselected patient population. The study was amended after first 75 randomised patients to allow inclusion of centrally confirmed *KRAS* mutation negative patients. After the amendment, the use of primary prophylactic G-CSF is mandatory and current toxicity management guidelines are being provided and amended based experience within the study D1532C00016.

Study D1532C00067

A phase I study of the combination of selumetinib and docetaxel (60mg/m^2) in Japanese patients is ongoing. It is investigating the pharmacokinetic profile of selumetinib, as well as the safety and tolerability of the combination. Preliminary data suggests that Japanese patients may have experienced a greater exposure to selumetinib than the majority of non-Asian patients treated in other studies. It is recommended that investigators take this information into consideration when dosing patients of Asian descent. If, during the course of this phase III study, the on-going phase I study, or another study, finds that the combination regimen is not tolerated in a specific ethnic group, this ethnic group may later be excluded from this phase III study. Investigators will be notified, and the protocol will be amended to reflect the findings.

Study D1532C00086

The pharmacokinetics of Selumetinib were investigated in study D1532C00086, conducted in the UK involving healthy volunteers of Asian ethnicity (defined as being born in an Asian country, and expatriate for not longer than 5 years, and with maternal and paternal grandparents of Asian ethnicity). The subjects who received Selumetinib in Study D1532C00086 were of the following ethnicities: Japanese, Chinese, Filipino, Malay, Malaysian, Maldivian, Singaporean, Thai, Indian and Vietnamese, and it is not known in these groups whether Selumetinib exposure will be similar to Western subjects or to subjects of the specific Asian ethnicities included in Study D1532C00086.

The pharmacokinetic findings from study D1532C00086 do not support excluding subjects of Asian ethnicity from studies of Selumetinib. However, as it is possible that Asian subjects may experience higher Selumetinib plasma exposure (than would be expected in Western subjects receiving the same dose of selumetinib), there could be a potential for a higher risk of adverse events.

The number of Asian patients with advanced cancer who have received treatment with Selumetinib is very low. Emerging information from ongoing study D1532C00067 of Japanese patients receiving selumetinib + docetaxel for second-line treatment of NSCLC suggests that febrile neutropenia may occur more commonly in Japanese patients (3 of 8 patients treated, although comparative data in Japanese patients receiving docetaxel

monotherapy is not available) than might be predicted from studies conducted in Western subjects.

Patients of Asian ethnicity are not excluded from studies evaluating Selumetinib. However, when considering enrolling an individual of Asian ethnicity to a Selumetinib clinical study, investigators should make a clinical judgment as to whether the potential risk of experiencing higher Selumetinib plasma levels outweighs the potential benefit of treatment with Selumetinib. The Patient Information and Consent form for studies of Selumetinib includes information on the possibility of higher Selumetinib plasma levels and occurrence of adverse events in Asian subjects than in subjects who are not of Asian origin. Investigators should be aware of the potentially higher risk of adverse events when monitoring patients of Asian ethnicity receiving treatment in clinical studies of Selumetinib.

1.1.6 Docetaxel

Docetaxel (TAXOTERE™, Sanofi-Aventis) is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of platinum-based chemotherapy. At a dose of 75 mg/m^2, docetaxel had a significant beneficial effect on OS compared with best supportive care, and a significantly higher 1-year survival compared to the control group of vinorelbine or ifosfamide (Shepherd et al 2000, Fossella et al 2000).

Expected toxicities include hypersensitivity reactions, febrile neutropenia, peripheral neuropathy, and fluid retention. Please refer to the docetaxel product information for a complete listing of adverse events associated with administration of docetaxel. The incidence of severe fluid retention can be reduced by treatment with dexamethasone for 3 days beginning the day before docetaxel administration. Dexamethasone should be given orally. Additional doses of intravenous dexamethasone can be given at the investigator's discretion. The local docetaxel product information may vary between countries and should be confirmed with the local dispensary.

1.2 Research hypothesis

Selumetinib 75 mg bd in combination with docetaxel 75 mg/m^2 administered every 21 days shows improved efficacy compared to placebo in combination with docetaxel in a placebo-controlled study of patients receiving second-line treatment for *KRAS* mutation-positive locally advanced or metastatic NSCLC.

1.3 Rationale for conducting this study

Pre-clinical studies with selumetinib and clinical experience to date suggest that cell lines and tumours with activating mutations in RAS/RAF/MEK/ERK transduction pathway may be particularly sensitive to MEK inhibition. Over-activation of this pathway has been implicated in numerous cancers, including NSCLC with *KRAS* mutations. These mutations are found in up to 50% of adenocarcinomas and to a lesser extent in squamous cell carcinomas (Somers et al 1999).

Selumetinib in combination with docetaxel has demonstrated clinical efficacy versus docetaxel alone (numerical increase in median OS, statistically significant improvements in secondary endpoints including PFS and response rate) in patients with *KRAS* mutation-positive advanced NSCLC (D1532C00016).

Pre-clinical experiments demonstrated superior anti-cancer effect when selumetinib was used in combination with docetaxel in cell lines harbouring *KRAS* mutations, as compared to monotherapy activity of each agent (Wilkinson et al 2008). In line with this observation and the results from the phase II combination study D1532C00016, the randomised phase III study SELECT-1 will confirm the efficacy of the selumetinib and docetaxel combination in patients with NSCLCs that harbour mutations of *KRAS* and are eligible for second-line treatment. Patients with *KRAS* mutation negative NSCLC will be randomised for study D1532C00064 (SELECT-2), also comparing the efficacy of selumetinib plus docetaxel to placebo plus docetaxel in a second line setting.
This approach will improve understanding of the response to the combination therapy and could provide a target therapy for a population who has few treatment options. The personalised medicine approach of pre-selecting patients offers an opportunity to maximise the chance of identifying therapeutic benefit (Pfister et al 2004).

This study will also assess the PK, safety, patient reported outcomes (PRO) and tolerability profile of the selumetinib/docetaxel combination, compared to placebo in combination with docetaxel, by monitoring of adverse events, safety assessments, symptom and HRQoL questionnaires and blood sampling for PK analysis.

As part of this study, *KRAS* tumour mutation status will be determined as a key entry criterion. However, the acquisition of tumour samples from this patient population is difficult. An alternative non-invasive approach would be to have a method of testing the *KRAS* mutation status derived from tumour DNA circulating in blood. It has been shown that it is possible to extract circulating tumour DNA from a significant proportion of patients with advanced NSCLC (Bremnes et al 2005). Therefore an investigation into the concordance between the mutation status derived from a tumour sample and that from a blood sample cfDNA will be performed. Data from blood samples will be generated at a later date and will not be used as an entry criterion for the study.

1.4 Benefit/risk and ethical assessment

Currently there are no effective targeted treatments for patients with NSCLCs that harbour a *KRAS* mutation. Medicines approved for unselected patients are prescribed however there are no therapies available which specifically target the genetic abnormality within this disease. As discussed above there are preclinical data supporting the use of selumetinib in combination with docetaxel for the treatment for *KRAS* mutation-positive NSCLC. These data are supported by the clinical data generated within the randomised placebo controlled study that showed that selumetinib in combination with docetaxel provided an unprecedented level of efficacy to patients with *KRAS* positive NSCLC. The use of the combination was associated with a greater toxicity burden however the various toxicities experienced were managed using conventional methods and there was no increase in deaths resultant from the adverse events.

Treating physicians conducting this clinical study will be informed of the tolerability issues their patients may experience and will be provided with management guidelines to minimise the duration and impact of such events (see Appendix I, 'Guidance for Management of Specific Adverse Events in Studies of Selumetinib'). Primary prophylactic pegylated G-CSF will be administered after every dose of docetaxel which should minimise the haematological toxicity experienced by patients participating in this study and may prolong the duration of possibly effective therapy. Investigators will be informed of the emerging data from other studies evaluating selumetinib in combination with docetaxel as treatment for NSCLC and other tumours, particularly those data that may assist delineation of the origin of toxicities. Furthermore, the benefit/risk for patients in this study will be assessed by an Independent Data Monitoring Committee (IDMC) via ongoing safety assessments.

AstraZeneca believes that selumetinib in combination with docetaxel may offer a positive benefit/risk profile when compared to that provided by docetaxel alone as 2nd line treatment for NSCLC that harboured a mutation of *KRAS* and that further clinical evaluation of the selumetinib in combination with docetaxel is ethically justified within this clinical study.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary objective	Outcome variables
To assess the efficacy in terms of PFS of selumetinib in combination with docetaxel, compared to placebo in combination with docetaxel	PFS using investigator site assessments according to RECIST 1.1

2.2 Secondary objectives

Secondary objectives	Outcome variables
To assess the efficacy of selumetinib in combination with docetaxel, compared with placebo in combination with docetaxel.	OS ORR using investigator site assessments according to RECIST 1.1 DoR using investigator site assessments according to RECIST 1.1

Secondary objectives	Outcome variables
To assess the efficacy of selumetinib in combination with docetaxel compared with placebo in combination with docetaxel on NSCLC symptoms.	ASBI of the six symptoms (appetite, fatigue, coughing, shortness of breath, blood in sputum and pain) in the LCSS will be used to assess: Time to symptom progression Symptom improvement rate
To assess the safety and tolerability profile of selumetinib in combination with docetaxel compared with placebo in combination with docetaxel	AEs Clinical chemistry, haematology and urinalysis Vital signs ECHO/MUGA Ophthalmological examination
To investigate the PK of selumetinib and N-desmethyl selumetinib when administered in combination with docetaxel (other selumetinib metabolites e.g. selumetinib amide, may also be assessed).	Where the data allow, derived PK parameters for selumetinib and N-desmethyl selumetinib will be produced which may include, but are not restricted to, Cmax and AUC

2.3 Exploratory objectives

Exploratory objectives	Outcome variables
To describe the impact of treatment (selumetinib in combination with docetaxel and with placebo in combination with docetaxel) and disease state on symptom distress and interference with activity levels as measured by the LCSS and HRQoL as measured by the SF-36v2	Changes within each of the two treatment groups in the individual items of the LCSS: – Symptom Distress – Interference with activity levels SF-36v2 will be used to describe changes in 8 domain scores: - Physical functioning - Role limitations due to physical health problems - Bodily pain - Social functioning - General mental health - Role limitations due to emotional problems - Vitality, energy or fatigue - General Health And the two component summary scores over time: - Physical component summary - Mental component summary
To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, AEs and/or safety parameters if deemed appropriate	Output from both graphical and/or appropriate PK/PD modelling techniques.

Exploratory objectives	Outcome variables
To investigate the use of cfDNA derived from plasma, for the analysis of *KRAS* mutation status at screening and treatment discontinuation	*KRAS* mutation status of plasma derived DNA from samples collected at screening and treatment discontinuation
To explore the influence of *KRAS* mutation subtypes on response to treatment	*KRAS* mutation subtype(s)
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)	Host genetic polymorphisms
To explore potential biomarkers in residual biological samples (e.g. tumour and/or plasma) which may influence development of cancer (and associated clinical characteristics) and/or response	Biomarkers of response and/or development of cancer
To investigate the health economic impact of treatment and the disease on hospital related recourse use and health state utility.	Exploratory variables include number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay. Health state utility derived from the HRQL instrument, the SF-36 v2

The exploratory objective analyses may be reported separately from the CSR.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

Approximately 500 *KRAS* mutation-positive patients receiving second line treatment for locally advanced or metastatic NSCLC will be recruited from approximately 220 centres globally. In order to randomise approximately 500 patients it is expected that an estimated 3332 patients will be enrolled.

Patients will be enrolled on the basis of their NSCLC treatment status. The *KRAS* mutation status of the patient's tumour must be determined prospectively by a central laboratory using the cobas® *KRAS* Mutation Test
under the IDE. The term *KRAS* mutation positive is used to refer to any sample where mutations in codon 12, 13 or 61 have

been detected. Patients whose tumour sample harbours a *KRAS* mutation and fulfil all eligibility criteria will be randomised in a ratio of 1:1 to receive selumetinib 75 mg bd in combination with docetaxel 75 mg/m^2 or placebo in combination with docetaxel 75 mg/m^2. All patients will also receive pegylated G-CSF at a minimum of 24 hours after the administration of every docetaxel dose and not within 14 days prior to the next docetaxel administration.

Patients will be stratified at randomisation based on their WHO Performance Status (1/0) and tumour histology (squamous/non-squamous). See Figure 2.

If the Investigator feels it is appropriate, patients may be given the option to consent for *KRAS* mutation status screening (at the designated central laboratory) prior to consenting to the main study. In this instance, archival tumour material should be provided for this assessment. Only data required for the *KRAS* mutation screening will be collected at this time such as demographic data, tumour status and prior cancer treatment. AE/SAE data collection is not required prior to main consent. If *KRAS* mutation positive status is confirmed, the patient should be given the option to consent to the main study and *KRAS* mutation screening will not need to be repeated during visit 1.

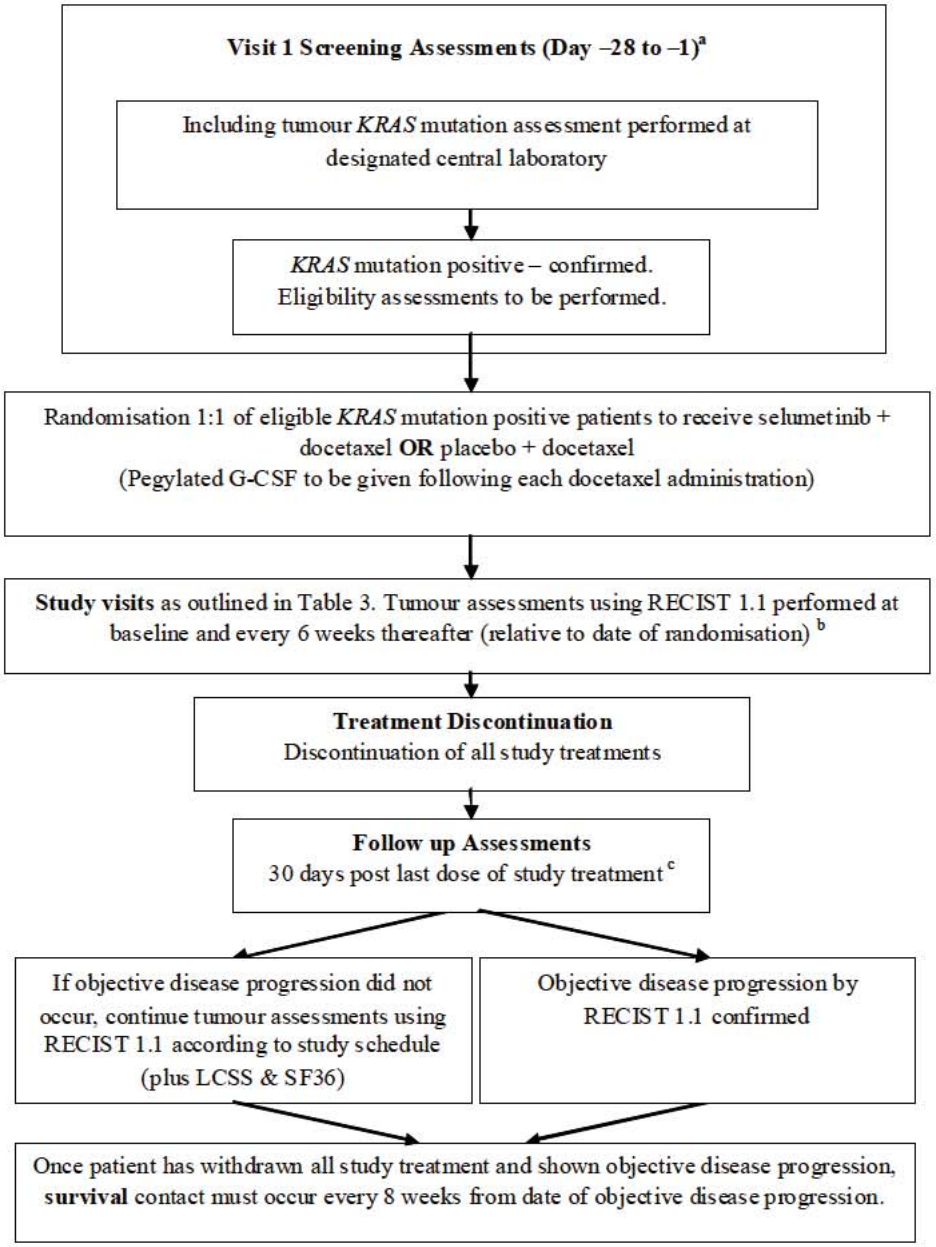
Patients will be seen and assessments performed as outlined in the Study Plan (Table 3) until objective disease progression or until meeting a criterion for discontinuation from study treatment (see Section 5.8) or from the study (See Section 5.9). See Sections starting at 3.1.1 for additional details on assessments and variables.

Patients may continue to receive study treatment (docetaxel, selumetinib/placebo), after objective disease progression if, in the opinion of the investigator, they are continuing to derive clinical benefit, in the absence of significant toxicity and it does not contravene local practice, after consultation with AZ. Patients remaining on study treatment beyond progression will continue to be seen as outlined in Table 3 and will have all required assessments performed excluding RECIST 1.1 assessments and PRO questionnaires (last scheduled PRO questionnaire is to be completed approximately 30 days after progression).

Once a patient has had objective disease progression recorded and discontinued all study treatment, they are to be followed up for survival status every 8 weeks until death, withdrawal of consent or the end of the study, whichever occurs first (Figure 2).

An IDMC will be established in order to assess the progress of the clinical trial, including reviewing the safety data. See Section 12.4 for further details.

Figure 2 Study flow chart



[a] Screening assessments can be performed in a stepwise process or in parallel to *KRAS* mutation assessment. Note: If the patient provides consent for *KRAS* mutation status screening (prior to the main study consent) *KRAS* mutation status will be tested by the designated central laboratory prior to visit 1.
[b] Up until the time of data cut off (DCO) for the analysis of PFS, patients must be followed until evidence of RECIST 1.1 defined progression (regardless of reason for treatment discontinuation)
[c] Last dose of selumetinib/placebo or docetaxel.

Table 3 Study Plan

Visit	Pre-screen (optional)	1	2	3	4	5	6	Treatment Visits **every 3 weeks (Visits 7+)**	If study treatment is discontinued AT disease progression			If study treatment is discontinued PRIOR TO disease progression				
		Screening Visit(s)	Randomise/ Baseline						Treatment discontinued	30 Day Follow-up	Survival Follow up **8 weekly**	Treatment discontinued	30 Day Follow-up	Progression follow-up **6 weekly**	30 Day post progression	Survival Follow up **8 weekly**
Day		-28 to 0	1	8	15	22	43	64+	**NA**			**NA**				
Week		-4 to 0	0	1	2	3	6	9+	**NA**			**NA**				
Window (days)	NA	NA		± 2				±7		±7			±7			
Consent for *KRAS* screening	X															
Main study consent		X														
Optional PGx consent		X														
Optional PGx sample			X													
Call IVRS/IWRS	X	X	X			X	X	X	X			X				
AEs and Con Meds		X	X	X	X	X	X	X	X	X		X	X			
Tumour material for *KRAS* test	X	X														
Demography, disease status	X	X														
Eligibility Criteria		X	X													
Medical/surgical history	X	X														
Smoking Status	X	X														
Pregnancy test		X	X	As clinically indicated [b]												
Tumour Evaluation (RECIST1.1)		X					X	6 weekly						6 weekly		
Ophthalmologic exam		X	X [b]							X[c]			X[c]			
Echocardiogram/MUGA		X	12 weekly and as clinically indicated [b]							X[c]			X[c]			

Table 3 Study Plan

Visit	Pre-screen (optional)	1	2	3	4	5	6	Treatment Visits **every 3 weeks (Visits 7+)**	If study treatment is discontinued AT disease progression			If study treatment is discontinued PRIOR TO disease progression				
		Screening Visit(s)	Randomise/ Baseline						Treatment discontinued	30 Day Follow-up	Survival Follow up **8 weekly**	Treatment discontinued	30 Day Follow-up	Progression follow-up **6 weekly**	30 Day post progression	Survival Follow up **8 weekly**
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**43**	**64+**	**NA**			**NA**				
Week		**-4 to 0**	**0**	**1**	**2**	**3**	**6**	**9+**	**NA**			**NA**				
Window (days)	**NA**	**NA**		**± 2**				±7		**±7**			**±7**			
Physical exam		X	X	X	X	X	X[d]	X [(d)]	X			X				
Vital signs		X	X	X	X	X	X	X	X	X[(c)]		X	X[(c)]			
Clinical Chem / Haematology[(a)]		X	X	X	X	X	X	X	X	X[(c)]		X	X[(c)]			
Urinalysis		X				X	X	X[(b)]								
ECG		X	X	X [(b)]						X[(c)]			X[(c)]			
WHO Performance Status		X	X			X	X	X	X			X				
Healthcare Resource Use			X	X	X	X	X	X	X	X		X	X	X	X	
PK plasma samples			X			X										
Biomarker plasma sample			X						X			X				
LCSS questionnaire			X	X	X	X	X	X	X	X		X	X	X	X	
SF-36v2 questionnaire			X				X	C5 D1[e]	X	X		X	X	X [(e)]	X	
Selumetinib dosing			Twice daily dosing													
Docetaxel dosing			X			X	X	X								
G-CSF (at a minimum of 24 hours **after** docetaxel dose)			X			X	X	X								
Drug accountability						X	X	X	X			X				

Table 3 Study Plan

Visit	Pre-screen (optional)	1	2	3	4	5	6	Treatment Visits **every 3 weeks (Visits 7+)**	If study treatment is discontinued AT disease progression			If study treatment is discontinued PRIOR TO disease progression				
		Screening Visit(s)	Randomise/ Baseline						Treatment discontinued	30 Day Follow-up	Survival Follow up **8 weekly**	Treatment discontinued	30 Day Follow-up	Progression follow-up **6 weekly**	30 Day post progression	Survival Follow up **8 weekly**
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**43**	**64+**	**NA**			**NA**				
Week		**-4 to 0**	**0**	**1**	**2**	**3**	**6**	**9+**	**NA**			**NA**				
Window (days)	**NA**	**NA**		**± 2**				±7		±7			±7			
Anti-cancer therapy		Not allowed during treatment phase								X	X		X	X	X	X
Survival contact											X					X

[a] All patients with AST, ALT or bilirubin ≥1.5 X ULN at the time of the last dose of selumetinib/placebo should have a further liver chemistry profile performed 30 days (±7 days) after permanent discontinuation of selumetinib/placebo;
[b] See Section 3.1.4 for assessments to be performed where clinically indicated during the treatment phase;
[c] See Section 3.1.5 for assessments to be performed where clinically indicated at the 30 day follow-up visit;
[d] Every 12 weeks if patient has discontinued docetaxel but continues on selumetinib/placebo
[e] SF-36v2 to be completed at baseline, at Cycles 3 and 5 Day 1during treatment, at treatment discontinuation, 30 days after treatment discontinuation, at time of progression, at each post progression follow up and 30 days post progression

3.1.1 Pre-screening Procedures

If the Investigator feels it is appropriate, patients may be given the option to consent for *KRAS* mutation status screening (at the designated central laboratory) prior to consenting to the main study. In this instance, archival tumour material should be provided for this assessment. Only data required for the *KRAS* mutation screening will be collected at this time such as demographic data, smoking status, tumour status and prior cancer treatment. AE/SAE data collection is not required prior to main consent. If *KRAS* mutation positive status is confirmed, the patient should be given the option to consent to the main study and *KRAS* mutation screening will not need to be repeated during visit 1.

Once consent for *KRAS* mutation screening has been signed, the PI or delegate, will contact Interactive Voice/Web Response System (IVRS/IWRS) to have the subject assigned a unique enrolment number registering the patient with status pre-screened (see Section 5.2). When the patient consents to the main study the PI or delegate will contact IVRS/IWRS to confirm that the main consent has been signed registering the patient as enrolled.

3.1.2 Screening Procedures

It is recommended the screening assessments be performed in a stepwise process beginning with the confirmation of *KRAS* mutation status as determined by the designated central laboratory. However, screening assessments may be done in parallel to the *KRAS* mutation assessment, as appropriate.

The following assessments will be performed and recorded in the patient's medical chart and electronic Case Report Form (eCRF), where appropriate, during screening as outlined in Study Plan (Table 3):

Written informed consent/Assignment of subject ID:

- Prior to the start of any study specific procedures, each patient must provide signed informed consent to the main study (see Section 8 for Ethics and Regulatory Requirements).
- Each patient will undergo screening procedures within 28 days prior to randomisation.
- Additionally, patients will be given the option to consent to the host pharmacogenetics research component of the study in a separate Informed Consent Form (ICF).

Contact IVRS/IWRS:

- Once consent has been signed, the PI or delegate, will contact IVRS/IWRS to have the subject assigned a unique enrolment number. If a patient has had an enrolment number assigned as part of the pre-screening procedures the same enrolment number should be used. If a subject withdraws from the pre-screen or main study, then the enrolment code cannot be reused. (See Section 5.2)

s and concomitant medication:

- AEs and concomitant medications will be collected from the time of signature of informed consent to the main study until 30 days (± 7 days) after the last dose of the last study treatment. See Sections 5.6 (concomitant medications) and 6.4 (adverse events).

Tumour sample and *KRAS* mutation status:

- Tumour sample must be formalin fixed paraffin embedded (FFPE) and may be archival or a fresh biopsy sample. Samples collected from primary or metastatic tumour deposits will be accepted. Sites should ship the tumour sample to the central laboratory as soon as it is available. Blocks must be provided wherever possible. In the event blocks cannot be provided, 20 fresh cut (within 1-2 days of shipping) sections of 5 microns can be shipped for mutation analysis. If 20 sections are not possible then there is a strong preference to provide at least 15 sections. The minimum number of sections required to perform eligibility assessments is 6 sections. See Section 3.1.9.1 and Figure 3.

- If a patient has a *KRAS* mutation positive status centrally confirmed as part of the pre-screen visit, this sample does not need to be provided again at visit 1.

Demography:

- Demography must be captured for all patients, including screen failures. Demographic data and other characteristics will include: date of birth (or age if locally data privacy laws prevent the capture of birth date), gender, race and ethnicity.

Eligibility criteria:

- Patients must not be randomised unless all eligibility criteria have been fully met. See Section 4.

Medical/surgical history:

- A standard medical and surgical history will be obtained.

Smoking Status:

- Details of the patients smoking status are to be provided as applicable.

Pregnancy test

- Pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) for women of childbearing potential only (See Section 4.1, #9).

Tumour Assessments (RECIST 1.1):

- The imaging modalities used for RECIST 1.1 assessments will be CT or MRI scans of chest and abdomen (including liver and adrenal glands). Any other sites where disease is suspected or known at baseline must be also imaged. Baseline assessments should be performed as close as possible to the start of treatment (and prior to randomisation). See Section 6.3.

Ophthalmologic exam:

- Measurements of best-corrected visual acuity, intraocular pressure and slit-lamp fundoscopy should be obtained. See Section 3.1.5 for safety considerations that may require ophthalmologic exams.

Echocardiogram/MUGA:

- Left ventricular ejection fraction (LVEF), end diastolic and end systolic left ventricular volumes should be recorded at each assessment. If an echocardiogram scan cannot be taken, a MUGA scan to assess LVEF will be conducted. See Section 3.1.5 for safety considerations that may require echocardiogram/MUGA assessments.

Physical exam, including vital signs (height, weight, body temperature):

- Physical examination includes an assessment of the following: general appearance, respiratory, cardiovascular, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.
- Height is only required at screening.
- Supine blood pressure (BP) and pulse will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size after 10 minutes rest.
- Temperature should be recorded in the case of febrile neutropenia/ neutropenia (CTCAE grade 3 or 4) and as clinically indicated.

Laboratory safety assessment

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

ECG:

- A single 12-lead ECG should be performed and 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 PI 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.

WHO PS must be assessed during Screening and at baseline using the WHO guidelines below and must be 0-1.

- 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.

3.1.3 Baseline/Randomisation Procedures

Once all eligibility has been confirmed, if the patient is deemed eligible, the PI or delegate will call IVRS/IWRS to randomise the subject & assign a unique randomisation code. See Section 5.2.1. Patients must not be randomised unless all eligibility criteria have been met.

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

The following additional assessments must also be conducted at baseline/randomisation:

Physical exam, including vital signs (height, weight, body temperature):

- Assessments to be performed as per the screening assessment, except for height, which is not required.

Patient Reported Outcome Questionnaires (LCSS and SF-36v2):

- Patients should be provided with a suitable, private place to complete the questionnaires alone (i.e. without assistance from clinic staff, relative or friend).

- PROs should be completed before any study related assessments. SF-36v2 should be completed after the LCSS when given on the same day. See Section 6.5.

PK (plasma):

- On PK sampling days, docetaxel and selumetinib/placebo dosing should not occur until the pre-dose PK samples have been taken. See Section 6.6.

Plasma for exploratory analysis of cfDNA:

- Patients will be requested to provide a plasma sample prior to randomisation and at the time of treatment discontinuation, see Section 6.9.2.

Pharmacogenetics (optional):

- Consent should be obtained at screening and the sample obtained at the baseline/randomisation visit; however, consent may be obtained and the sample may be taken at any time until the patient's last visit. See Section 6.8.1.

G-CSF Administration (post docetaxel administration):

- G-CSF must be administered at a minimum of 24 hours after the administration of docetaxel and not within 14 days prior to the next docetaxel administration. Patient booklets may be used to capture dosing dates and times.

3.1.4 On Study Procedures

Assessments during the study will be completed as outlined in Study Plan (Table 3) and as described, where applicable, in Section 3.1.3.

Pregnancy:

- Investigator should assess the patient's compliance to contraceptive measures and perform a test if required.

- In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

CT/MRI Tumour Assessments (RECIST 1.1):

- To be performed at visit 6 then at every 6 weeks thereafter until objective disease progression. It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled visit ± 1 week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Any other sites at which new disease is suspected should also be appropriately imaged.

Ophthalmologic examination:

- To be performed where clinically indicated.

Echocardiogram/MUGA:

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

Physical exam:

- To be performed at every visit up to and including the treatment discontinuation visit. Following the discontinuation of docetaxel and whilst remaining on selumetinib/placebo, assessments of physical exam may decrease in frequency to every 12 weeks, relevant to Day 1.
- Data are not required to be captured on an eCRF, however any significant changes from baseline (if baseline physical was completed) or screening (if no baseline physical was completed) must be reported as an AE.

Vital signs (including BP, weight, body temperature):

- To be performed at every visit up to and including the treatment discontinuation visit.
- Supine blood pressure and pulse will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size after 10 minutes rest.
- Temperature should be recorded in the case of febrile neutropenia/ neutropenia (CTCAE grade 3 or 4) and as clinically indicated.

Laboratory safety assessment

- Blood samples for determination of clinical chemistry and haematology, will be taken at every visit up to and including the treatment discontinuation visit.

Urinalysis:

- Urine analyses (dipstick) should be performed before docetaxel administration on cycles 2 & 3 (i.e. week 3 and 6) and at any other visit where clinically indicated.

ECG:

- If an abnormal ECG finding at baseline is considered by the investigator to be clinically significant, it should be reported as a concurrent condition.
- To be performed where clinically indicated. During the study, clinically significant abnormal ECG findings not present at baseline should be reported as an AE. If present, the clinical signs and symptoms associated with the abnormal finding

should be reported as the AE with the ECG abnormality given as explanatory information.

Performance Status:

- To be assessed using the WHO guidelines at visits 5, 6, then at every visit up to and including the treatment discontinuation visit.

PK (plasma):

- Venous blood samples to be taken at visit 5 at the time points detailed in Section 6.6.1.

Patient Reported Outcome Questionnaires (LCSS and SF-36v2):

- LCSS to be completed before any study assessments at each visit up to and including the treatment discontinuation visit.

- SF-36v2 to be completed before any study assessments at cycles 3 & 5 day 1 only.

Patients will follow Table 3 until objective disease progression or until meeting any other discontinuation criteria as outlined in Section 5.8. Please see Section 3.1.6 for the assessments required at discontinuation.

3.1.5 Additional On-Study Safety Procedures

Refer to Section 5.5.6 and Appendix I, 'Guidance for Management of Specific Adverse Events in Studies of Selumetinib' for information on the management of AEs for patients on selumetinib. The following situations require additional safety monitoring:

- All cardiorespiratory AEs with no obvious diagnosis should be assessed with a single ECG, ECHO/MUGA, vital signs (resting BP, pulse rate), weight and blood samples for Troponin (isoform per institution norm) taken at the time of the event.

- Measurements of Troponin (isoform per institution norm) and recording single ECG to be performed when there is a significant drop in LVEF (decrease by > or equal 10 percentage points and to an absolute value < 55%). Patients should be managed according to the algorithm provided in Appendix I "Guidance for Management of Specific Adverse Events in Studies of Selumetinib".

- All new dyspnoea AEs or worsening of pre-existing dyspnoea AEs should be investigated according to the algorithm provided in Appendix I, 'Guidance for Management of Specific Adverse Events in Studies of Selumetinib'.

- If a patient experiences an AE of visual disturbance (including blurring of vision) an ophthalmologic examination (including best corrected visual acuity, intraocular pressure, slit lamp fundoscopy and with consideration of additional tests if clinically indicated e.g. fundus photography if abnormality detected or optical coherence

tomography [OCT] scan) must be performed and the AE managed accordingly to Appendix I, 'Guidance for Management of Specific Adverse Events in Studies of Selumetinib'.

- Specific guidance for adverse event management, interruption or reduction of treatment with selumetinib may be considered in occurrence of events of rash, stomatitis or diarrhoea as indicated in the algorithms provided in Appendix I, 'Guidance for Management of Specific Adverse Events in Studies of Selumetinib'.

- Hyperphosphatemia and increase in the calcium phosphate product should be managed according to local practice.

- If muscle weakness, myalgia (muscle pain) occurs that cannot be explained the patient should have a neuromuscular examination, urine analysis and CPK measurement performed (with where possible an additional CPK-MM) and be managed according to local practice.

3.1.6 Discontinuation Procedures

Patients may discontinue from study treatment or from the study for the reasons outlined in Sections 5.8 (study treatment) and 5.9 (study). Depending on when a patient discontinues (before or after progression), which study treatment is discontinued (selumetinib/placebo, docetaxel, or both), and the reasons why, different assessments may be required.

Patients will be evaluated until objective disease progression by RECIST 1.1, as per the study plan (See Table 3) and then followed for survival, regardless of whether study treatment is discontinued or delayed, new treatment is administered and/or in the case of protocol violations, unless they withdraw consent.

Once patients on selumetinib/placebo have been discontinued from treatment, other treatment options will be at the discretion of the investigator. No cross over to selumetinib is permitted.

Patients who have a retinal abnormality prior to or at time of discontinuation of selumetinib/placebo should, if practicable, have a follow up eye examination performed 30 days after discontinuation of selumetinib/placebo in order to document reversibility.

Patients who had a drop in LVEF >10% from baseline and an absolute value <55% prior to or at the time of discontinuation of selumetinib/placebo should, where possible, have a follow up echocardiogram/MUGA, single ECG, and vital signs (including weight) performed 30 days after permanent discontinuation of selumetinib/placebo in order to document reversibility.

All patients with AST, ALT or bilirubin ≥1.5 X ULN at the time of the last dose of selumetinib/placebo should have a further liver chemistry profile performed 30 days (±7 days) after permanent discontinuation of selumetinib/placebo.

Drug accountability should continue to be performed until the patient stops all study treatment completely.

ontinuation of All Study Treatment Due to Disease Progression

Patients who discontinue all study treatment at the time of disease progression should be seen as soon as possible after their last dose of the last study drug and have assessments performed as outlined in Table 3. Following the treatment discontinuation visit, patients should attend a visit 30 days (±7 days) after discontinuation (See Section 3.1.7) and then be followed up for survival every 8 weeks (See Section 3.1.8).

3.1.6.2 Discontinuation of All Study Treatment Prior to Disease Progression

Patients who discontinue all study treatment prior to disease progression must continue to be seen and have RECIST 1.1 assessments performed every 6 weeks until disease progression. LCSS questionnaire should also be completed at each visit.

30 days (±7 days) after objective disease progression patients should complete the LCSS & SF-36v2 questionnaires and have their anti-cancer therapy details collected and then should be followed for survival (See Section 3.1.7). Refer to Table 3.

3.1.6.3 Discontinuation of Selumetinib/Placebo Only

Patients who discontinue selumetinib/placebo and remain on docetaxel should continue to be seen and have assessments performed every 3 weeks when docetaxel treatment is planned, as outlined in Table 3. Once docetaxel treatment is permanently discontinued, study visits should be performed as outline in either Section 3.1.6.1 or 3.1.6.2.

3.1.6.4 Discontinuation of Docetaxel Only

Patients who discontinue docetaxel and remain on selumetinib/placebo should continue to be seen and have assessments performed every 3 weeks as outlined in Table 3. Once selumetinib/placebo treatment is permanently discontinued, study visits should be performed as outline in either Section 3.1.6.1 or 3.1.6.2.

3.1.7 30 Day Follow Up

A follow-up visit should be conducted 30 days (± 7 days) after the last dose of study treatment (selumetinib/placebo or docetaxel). Any serious and/or non-serious AEs ongoing at the time of the treatment discontinuation visit or which have occurred during the defined 30-day follow-up period must be followed-up (in accordance with Sections 6.4.3 and 6.4.4). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the eCRF. The assessments to be carried out at the 30-day follow up visit are detailed in the study plan (Table 3).

3.1.8 Survival Follow Up

Assessments for survival should be made every 8 weeks following objective disease progression. Survival information may be obtained via telephone contact with the patient,

patient's family or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected. Survival data will be collected up to the time of the final OS analysis.

In addition, patients should be contacted in the two weeks following the data cut-off for the final survival analyses to provide complete survival data.

The status of the patient at the time of an overall survival analysis should be obtained by the site personnel from publicly available death registries in the event that a patient has withdrawn from the study or are "lost to follow up". In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

3.1.9 Determination of *KRAS* mutation status

3.1.9.1 Tissue sample

In order to participate in this study, each patient must have the *KRAS* mutation status of a tumour sample determined by the designated central laboratory. Informed consent will be obtained and a tumour sample for determination of *KRAS* mutation retrieved and transported for testing. The tumour sample provided for *KRAS* testing must be formalin fixed and paraffin embedded and may be either an archival sample or a fresh biopsy (taken if the investigator deems this to be appropriate).

KRAS mutation status will be determined using the cobas® *KRAS* Mutation Test and reported to the investigator within 5 working days of sample receipt. Patients with confirmed *KRAS* mutation-positive NSCLC tumour sample may proceed to randomisation provided all other eligibility criteria are satisfied.

Blocks must be provided wherever possible. In the event blocks cannot be provided, 20 fresh cut (within 1-2 days of shipping) sections of 5 microns can be shipped for mutation analysis. If 20 sections are not possible then there is a strong preference to provide at least 15 sections. The minimum number of sections required to perform eligibility assessments is 6 sections. Samples collected from primary or metastatic tumour deposits will be accepted. Bone and cytology samples (even if FFPE) are not acceptable.

If histopathological review shows the initial tumour sample to be of a poor quality, if sufficient DNA cannot be extracted from the sample to perform *KRAS* testing, or the central laboratory is unable to report a result from the initial tumour sample, a second tumour sample should be submitted for testing. In order to optimise the chance of obtaining sufficient good quality DNA to identify the *KRAS* mutation status, it is recommended that the investigator submit a fresh FFPE biopsy sample, where possible. In case of a failure to determine *KRAS* mutation status following testing of a second sample and according to the testing algorithm provided by , no further testing will be permitted and such patients will not be eligible. See Figure 3 for further details.

Where a second tumour sample is submitted, the *KRAS* mutation status will be reported to the investigator within 5 working days of sample receipt. Therefore the impact of this on the screening assessment timings should be considered. All screening assessments must still be completed within the 28-day screening period.

Patients whose tumours have been previously tested and found positive for either *EGFR* mutations or *ALK* translocations should not be considered eligible for this study and samples should not be submitted for testing for *KRAS* mutations as they are mutually exclusive.

A two-stage consent process will allow patients currently on first-line treatment to provide a separate consent to enable their tumour *KRAS* mutation status to be established in advance of completion of their first-line treatment. An archival tumour sample should be provided for this assessment. A second archival tumour sample can be submitted for testing if the laboratory is unable to report a result from the initial tumour sample as part of the pre-screening. The same patient will not be retested if a valid result has been obtained from the initial tumour sample. If *KRAS* mutation positive is confirmed, on completion of the first line treatment, the patient may be enrolled onto the study after signing the main consent form.

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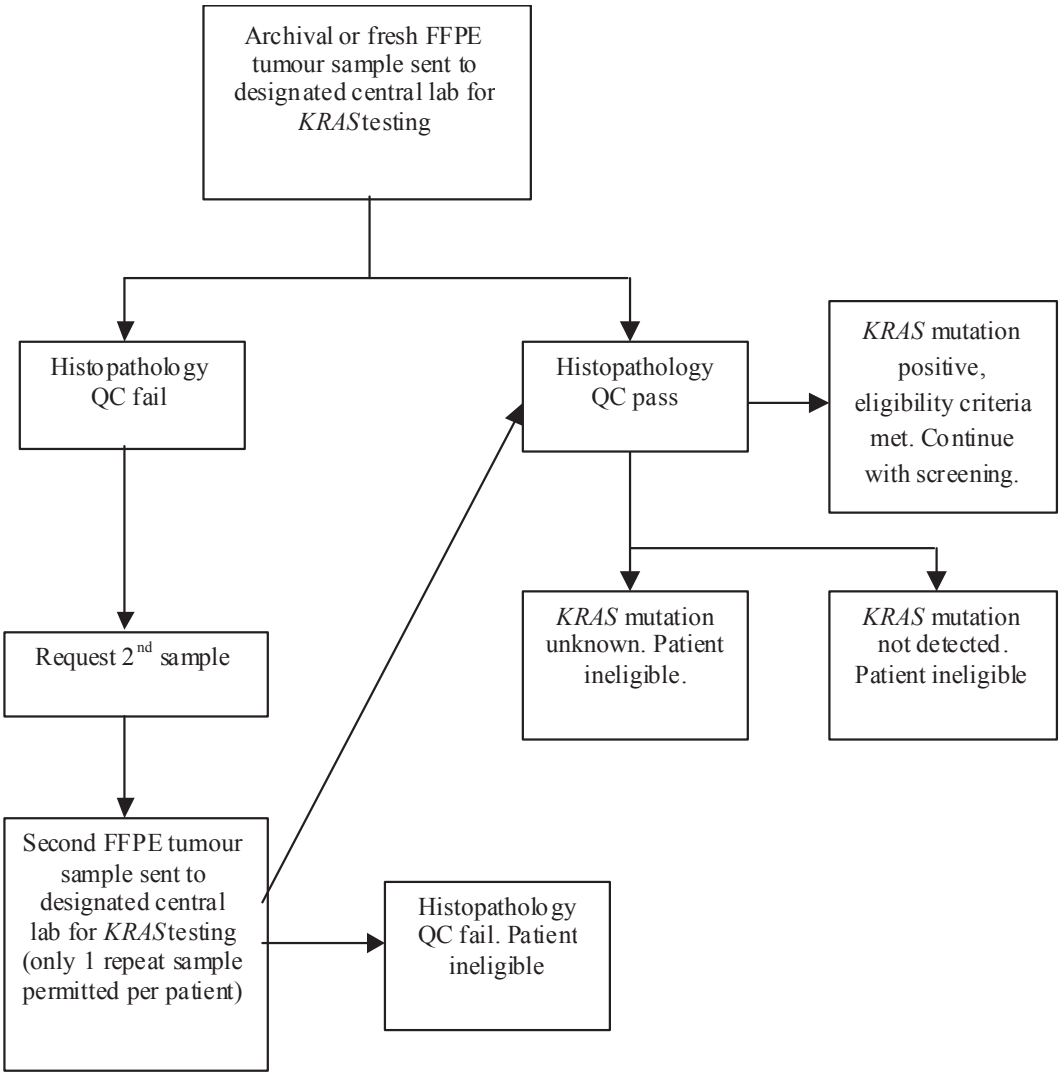
3.1.9.2 Blood sample

Blood samples for exploratory assessments plasma cfDNA will be collected for all patients prior to randomisation and following discontinuation of selumetinib/placebo.

Figure 3 Algorithm for central laboratory *KRAS* mutation testing



3.2 Rationale for study design, doses and control groups

3.2.1 Rationale for study design

The study design is randomised and double-blinded in order to minimise bias when assessing whether selumetinib in combination with docetaxel shows better efficacy than placebo in combination with docetaxel.

The primary endpoint is PFS in this study, rather than overall survival. This is justified by the increasing prevalence of 3rd-line therapies that are available for patients who have disease progression after 2nd-line treatment. These subsequent therapies are likely to impact the overall survival outcome, independent of the effects of selumetinib in the 2nd-line setting. Furthermore, regional and other variations in the standard of care may result in imbalances in the subsequent therapy received by subjects in the 2 treatment arms of the study.

However, this study is sized to characterise the overall survival benefit of selumetinib in combination with docetaxel. This study includes overall survival as a secondary endpoint, and all subjects will be followed for survival. In addition, the study includes other measures of clinical benefit, including response rate, duration of response, and measures of health-related quality of life, to provide supportive data on the benefit of selumetinib.

Patients may continue to receive study treatment whilst, in the opinion of the investigator, they are continuing to receive clinical benefit in the absence of unacceptable toxicity, despite having objective disease progression. This allows a patient to derive clinical benefit for a longer time period and potentially improve their overall survival. There is no crossover of treatment groups permitted, as this would necessitate unblinding of the randomisation code and confound the analysis of overall survival.

The use of placebo control in this study provides for a robust assessment of the benefit of selumetinib in combination with docetaxel, and is considered appropriate in this subject population because docetaxel is approved for use as a single-agent in the 2nd-line treatment of patients with NSCLC. Docetaxel is one of the most commonly prescribed drugs in second-line NSCLC, and remains a recognised standard of care in this setting (Pfister et al 2004; Azzoli et al 2011). As such all patients, including those randomised to the placebo/docetaxel arm, will be receiving an approved second line therapy for NSCLC.

The final analysis will be conducted when approximately 325 deaths have been reached.

3.2.2 Rationale for dosing

Selumetinib will be initially administered at a dose of 75mg twice daily. This is the recommended dose for administration as both monotherapy and in combination with docetaxel as defined in phase I multiple ascending dose studies and subsequent phase II studies.

Docetaxel has been selected as the combination and comparator agent for this study as it is one of the most commonly prescribed drugs in second-line NSCLC, and remains a recognised standard of care in this setting (Pfister et al 2004; Azzoli et al 2011). The 75mg/m^2 dose of

docetaxel selected is the licensed dose for patients with previously treated NSCLC and was the dose tested in combination with selumetinib in the completed phase I study (D1532C00004) and the completed phase II study (D1532C00016). See Section 1.1.5.

3.2.3 Rationale for mandatory administration of pegylated G-CSF

In order to improve the benefit/risk ratio that may be expected by patients receiving therapy in either arm of this double blind randomised study pegylated G-CSF will be administered after every chemotherapy dose, at a minimum of 24 hours after the administration of docetaxel and not within 14 days prior to the next docetaxel administration.

Patients receiving 2nd line therapy for NSCLC have been exposed to chemotherapy agents in the 1st line setting. They may therefore already have underlying bone marrow depletion and be at increased risk of haematological toxicity from cytotoxic agents. Patients who received either docetaxel monotherapy or docetaxel in combination with selumetinib in the completed phase II Study D1532C00016 experienced such haematological toxicity. This was more frequent and severe in patients who received the combination with 17% experiencing an episode of febrile neutropenia. American Society of Clinical Oncology (ASCO) guidelines (ASCO 2006) recommend the administration of primary prophylactic G-CSF if a regimen is likely to induce a 20% or greater incidence of febrile neutropenia. In Study 16 the incidence of febrile neutropenia/neutropenic infection was 18.2% (8/44) for selumetinib+docetaxel vs 0% in placebo+docetaxel group.

In order to minimise the possibility of a failure to administer G-CSF and to maximise patient convenience a pegylated form of G-CSF will be mandated in this study. No clear evidence exists to demonstrate that any particular preparation of G-CSF is superior to the others however guidelines issued by the EORTC (Aapro et al. 2011) state “evidence from multiple low level studies derived from audit data and clinical practice suggests that some patients receive suboptimal daily G-CSFs; the use of pegfilgrastim may avoid this problem.”

3.2.4 Rationale for PK

Currently a correlation between plasma concentrations and pharmacodynamic parameters of clinical efficacy has not been established. PK samples have been collected in a previous NSCLC study in patients with *KRAS* mutation tumours however there were insufficient samples to enable a correlation to be established. Plasma concentration data generated in this study will be combined with data from previous studies and used to build a PK/PD model to aid understanding of the link between plasma concentration and efficacy

3.2.5 Rationale for exploratory biomarkers (cfDNA)

Prior to randomisation and at the time of treatment discontinuation, patients will be requested to provide a plasma sample. These samples will be used for the extraction and analysis of cfDNA. The cfDNA will be used for the analysis of *KRAS* mutation status in NSCLC patients with the aim of validating a less invasive / tumour independent approach to mutation analysis. cfDNA may also be utilised to assess the prevalence of other tumour related mutations. 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 samples for analysis in the future.

3.2.6 Rationale for pharmacogenetics (optional)

See appendix D 'Pharmacogenetics Research'.

3.2.7 Rationale for Exploratory Analysis of Residual Tumour Tissue

The objective of this research is to collect and store tumour tissue for future exploratory research into genes, RNAs (mRNA and micro RNA) and proteins that may influence response to selumetinib and agents used in combination.

3.2.8 Rationale for Patient-Reported Outcomes

In addition to assessing survival in oncology clinical trials it is important to understand how patients feel and function. This will be addressed by symptom assessment as well as HRQoL assessment throughout the study. As many patients will be symptomatic as they enter the study, assessment of their NSCLC symptoms will support the efficacy evaluation.

In the phase II Study D1532C00016, *post hoc* analysis of disease-related symptoms based on the LCS, showed that significantly more patients treated with the selumetinib plus docetaxel combination experienced clinically important improvements in LCS compared with placebo plus docetaxel, with LCS improvement rates of 44% and 25%, respectively.

The main purpose of the HRQoL assessment is to show the overall influence of the benefits and toxicity of the treatment from a patient perspective and to aid understanding of the risk-benefit evaluation. The PRO instruments selected for inclusion in the study are well-established instruments that have been previously included in lung cancer clinical trials. The LCSS was selected because it includes the most relevant symptoms of NSCLC. The instrument was developed specifically for use in lung cancer studies and has been shown to be valid, reliable and responsive to changes in underlying lung cancer (Burke et al, 1985; Monras et al, 1985; Hollen et al, 1994).

The SF-36v2 is the most widely used generic measure of HRQoL/health status covering broad aspects of HRQoL and has been demonstrated to have strong validity and reliability.

3.2.9 Rationale for health economic data

The assessment of health economic resource use data and derivation of health state utility from the SF-36v2 will provide important information for payers and will be used within economic evaluations of selumetinib.

4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

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

4.1 Inclusion criteria

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

1. Provision of informed consent prior to any study specific procedures

2. Male or female, aged 18 years or older

3. Histological or cytological confirmation of locally advanced or metastatic NSCLC (IIIB-IV)

4. Failure of 1st line anti-cancer therapy (either radiological documentation of disease progression or due to toxicity) in advanced disease or subsequent relapse of disease following 1st line therapy. Patients who received adjuvant/neoadjuvant chemotherapy and develop a recurrence, with evidence of stage IIIB-IV disease within 6 months of completing chemotherapy, may be eligible. See Appendix G for further details

5. WHO Performance Status 0 – 1

6. Patients must be eligible to receive treatment with docetaxel in accordance with local prescribing information

7. 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 measurements.

8. *KRAS* mutation positive tumour sample as determined by the designated testing laboratory

9. Evidence of post-menopausal status, or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered postmenopausal if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

    – Women less than 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) levels in the post-menopausal range for the institution.

– Women over 50 years of age would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, radiation-induced oophorectomy with last menses > 1 year ago, chemotherapy-induced menopause with >1 year interval since last menses, or surgical sterilisation (bilateral oophorectomy or hysterectomy).

10. Serum creatinine clearance >50mL/min by Cockcroft-Gault formula (see Appendix H)

11. Patients should be able to swallow selumetinib/placebo capsules

12. Patients should be eligible to receive treatment with G-CSF medication in accordance with local prescribing information

13. Patients should be able to complete the PRO instruments in the available language versions

4.1.1 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.

4.2 Exclusion criteria

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

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

2. Previous randomisation in the present study

3. Mixed small cell and non-small cell lung cancer histology

4. Received >1 prior anti-cancer drug regimen for advanced or metastatic NSCLC. Patients who develop disease progression while on switch maintenance therapy (maintenance using an agent not in the first-line regimen) will not be eligible

5. Having received an investigational drug within 30 days of first dose of study treatment or within five half-lives of the compound or have not recovered from side effects of an investigational drug
Receiving or have received systemic anti-cancer therapy within 30 days prior to starting study treatment

6. Other concomitant anti-cancer therapy agents except steroids

7. Prior treatment with a MEK inhibitor or any docetaxel-containing regimen (prior treatment with paclitaxel is acceptable)

8. Any unresolved toxicity > or equal CTCAE Grade 2 from previous anti-cancer therapy, apart from alopecia

9. The last radiation therapy within 4 weeks prior to starting study treatment, or limited field of radiation for palliation within 7 days of the first dose of study treatment

10. Recent major surgery within 4 weeks prior to entry into the study (excluding the placement of vascular access) which would prevent administration of study treatment

11. History of hypersensitivity to selumetinib, docetaxel, pegylated G-CSF or any excipient of these agents

12. Symptomatic brain metastases or spinal cord compression. Patients with asymptomatic brain metastasis, or treated and stable off steroids and anti-convulsants for at least 1 month prior to entry into the study are eligible

13. Laboratory values as listed below (from laboratory results at Visit 1):

    – ANC < 1.5 x 10^9/L (1500 per mm^3)

    – Platelets < 100 x 10^9/L (100,000 per mm^3)

    – Haemoglobin ≤ 9.0 g/dL

    – Serum bilirubin > 1.5 x Upper Limit of Normal (ULN)

      This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of evidence of haemolysis or hepatic pathology), who will be allowed in consultation with their physician

    – AST or ALT in patients with no liver metastasis: > 2.5 x ULN

    – AST or ALT in patients with liver metastasis > 5 x ULN

    – AST or ALT > 3.5 x ULN and < 5 x ULN in patients with liver metastasis and ALP > 6 x ULN

14. Cardiac conditions as follows:

- Uncontrolled hypertension (BP ≥ 150/95 mmHg despite medical therapy)
- Acute coronary syndrome within 6 months prior to starting treatment
- Uncontrolled Angina - Canadian Cardiovascular Society grade II-IV despite medical therapy (Appendix K)
- Symptomatic heart failure (NYHA Class II-IV prior or current cardiomyopathy, or severe valvular heart disease, see Appendix K)
- Prior or current cardiomyopathy
- Baseline LVEF < 55% measured by echocardiography or Multi Gated Acquisition Scan (MUGA). Appropriate correction to be used if a MUGA is performed.
- Severe valvular heart disease
- Atrial fibrillation with a ventricular rate >100 bpm on ECG at rest

15. Any evidence of severe or uncontrolled systemic disease, active infection, active bleeding diatheses or renal transplant, including any patient known to have hepatitis B, hepatitis C or human immunodeficiency virus (HIV)

16. Refractory nausea and vomiting, chronic gastrointestinal diseases (e.g., inflammatory bowel disease), or significant bowel resection that would preclude adequate absorption

17. 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

18. Ophthalmologic conditions:

- Current or past history of central serous retinopathy
- Current or past history of retinal vein occlusion
- Intraocular pressure (IOP) > 21 mmHg or uncontrolled glaucoma (irrespective of IOP)

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

20. Clinical judgement by the investigator that the patient should not participate in the study.

4.2.1 Genetics research study (optional)

Exclusion criteria for participation in the optional genetics research component of the study:

1. Previous allogeneic bone marrow transplant

2. Whole blood transfusion within 120 days of the date of host genetic sample collection (except for leukocyte depleted blood transfusion, which is allowed).

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

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

1. Females of childbearing 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 agent. Selumetinib should not be administered to pregnant or breast-feeding women and conception while on treatment must be avoided.

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 agent.

3. Male and females of childbearing potential: reliable methods of contraception should be used consistently and correctly.

   - Acceptable methods of contraception for selumetinib for women 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).

   - Acceptable methods of contraception for selumetinib for men include the use of condoms, spermicidal foams or prior vasectomy.

   - True sexual abstinence is also an acceptable method of contraception (for both men and women) according to international recommendations.

   For patients receiving docetaxel, the reliable methods of contraception chosen should also be in accordance with the docetaxel national label.

4. Selumetinib/placebo 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), as described in Section 5.5.2. On clinic days on which PK samples are scheduled, dosing should be delayed until arrival at the clinic and until the pre-dose PK sample has been taken .

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

6. Patients should not donate blood whilst participating in this study and for 3 months following the last dose selumetinib/placebo and in accordance with the docetaxel local prescribing information after the last dose of docetaxel

7. During the study patients may receive palliative radiotherapy at the site of bone metastases that were present at baseline, providing the investigator does not feel that the bone pain is indicative of clinical disease progression. If a patient has further bone pain for which a second course of palliative radiation therapy is considered, the patient should be discussed with the AstraZeneca Study Team Physician to decide if it is necessary for a patient to be discontinued from study therapy. The need for radiotherapy to any other site should be discussed with the AstraZeneca Study Team Physician and any decisions will be made on a case-by-case basis.

8. Patients should be made aware of the need for oral care during the study. See Appendix I 'Guidance for Management of Specific Adverse Events in Studies of Selumetinib' Section 6 for further details.

Please refer to Section 5.6 for all restrictions relating to concomitant medications.

5.2 Patient enrolment and randomisation

At visit 1*, the PI or suitably trained delegate will:

1. Obtain signed informed consent (main study) from the potential patient before any study specific procedures are performed.

2. Assign potential patients a unique 7-digit enrolment code obtained through IVRS/IWRS. [(ECCNNXXX: CC being the country code. NN being the centre number, XXX being the patient enrolment code at the centre). Enrolment codes will start at 501 in each centre and go up sequentially (e.g., at Centre 01, patients will be assigned E codes E0101501, E0101502, etc)]

3. Determine patient eligibility. See Sections 4.1 and 4.2

At visit 2 once the patient is confirmed to be eligible, the PI or suitably trained delegate will:

4. Call IVRS/IWRS to assign eligible patient a unique randomisation code (patient number). Randomisation codes will start at 001 and will be assigned strictly sequentially by IVRS/IWRS, as patients are eligible for randomisation. This number is the patient's unique identifier and is used to identify the patient on the eCRFs.

*Note: patients who provide consent to *KRAS* mutation status screening prior to the main study consent will have their enrolment code assigned via IVRS/IWRS prior to visit 1 registering the patient with status "pre-screened". If *KRAS* mutation positive status is confirmed the patient may proceed into the main study. As soon as the patient has signed the main consent the PI or delegate will contact IVRS/IWRS to confirm that the main consent has been signed registering the patient as enrolled.

5.2.1 Procedures for randomisation (visit 2)

Patients must not be randomised unless all eligibility criteria have been met.

At Visit 2, patients who satisfy all the entry criteria will be centrally assigned to study treatment by the IVRS/IWRS, according to the randomisation scheme generated by the Biostatistics Group, AstraZeneca or delegate.

Patients will be randomised in a 1:1 ratio to either selumetinib 75mg bd in combination with docetaxel 75 mg/m^2 or matching placebo bd in combination with docetaxel 75 mg/m^2. Patients will be stratified at randomisation based on their WHO Performance Status (1/0) and tumour histology (squamous/non-squamous).

The actual treatment given to patients will be determined by the randomisation scheme in IVRS/IWRS. The randomisation scheme will be produced by a computer software program called GRand (AZ Global Randomisation system) that incorporates a standard procedure for generating randomisation numbers. One randomisation list will be produced for each of the four randomisation strata. A blocked randomisation will be generated and all centres will use the same list in order to minimise any imbalance in the number of patients assigned to each treatment group

Patients will be identified to the Centralised Randomisation Centre using patient initials, E-code and date of birth. Patients will be randomised strictly sequentially with each stratum, as patients are eligible for randomisation. The IVRS/IWRS Centralised Randomisation Centre will inform the investigator of the Kit ID number to be allocated to the patient at the randomisation visit.

Every effort should be made to minimise the time between randomisation and starting treatment. It is recommended that patients commence study treatment as soon as possible after randomisation.

The investigator will call/log in to the IVRS/IWRS for each subsequent dispensing visit for assignment of a new Kit ID number.

The Kit ID number dispensed at each visit will correspond to the treatment to which the patient was originally randomised.

If a patient discontinues participation in the study, then their enrolment/randomisation code cannot be reused.

5.3 Procedures for handling patients incorrectly enrolled or randomised or 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 randomised, 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. In situations where an agreement cannot be reached, the patient should have their study therapy stopped, then followed up for safety PFS and OS where possible as per Sections 3.1.8 and 5.8.1. Those patients randomised in error should remain in the study and be followed for progression free survival and overall survival where possible.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The study will be conducted in a double blinded fashion.

The selumetinib and placebo capsules will appear identical and presented in the same packaging to ensure blinding of the medication. Medication packs will be labelled using a unique medication identification number which is linked to the randomisation scheme. IVRS/IWRS will allocate randomisation numbers sequentially within each strata when sites call IVRS/IWRS to randomise an eligible patient. IVRS/IWRS will allocate the medication pack codes for selumetinib/placebo to be dispensed to the patient.

5.4.2 Methods for unblinding the study treatment

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Procedures for this will be described in the IVRS/IWRS user manual that will be provided to each centre, including emergency procedures that should be followed in the event that both IVRS and IWRS are down and unavailable for emergency unblinding.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The

investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

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

The randomisation scheme will also be made available to the bioanalyst to enable the analysis of samples from subjects who have received selumetinib to be prioritised. This documentation will be kept in a secure location until the end of the study.

Any plasma concentration data forwarded to the Clinical Pharmacology and Pharmacometrics Department will not reveal the identity of the patients.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Selumetinib Hyd-Sulphate	Blue capsule 25 mg	AstraZeneca
Placebo to match selumetinib	Blue capsule	AstraZeneca

5.5.2 Doses and treatment regimens – Selumetinib/Placebo

Selumetinib/placebo will be supplied in bottles of 60 capsules of 25 mg strength. At each dispensing visit, sufficient selumetinib/placebo for 21 days treatment, plus overage, will be dispensed. Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

Patients should swallow three selumetinib/placebo 25 mg capsules twice daily, commencing on Day 1 after required Day 1 assessments are completed. Capsules should be taken whole and with approximately 240 mL water.

The initial dose of selumetinib/placebo can be reduced/adjusted under circumstances described in Section 5.5.6.

All doses of selumetinib/placebo 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).

On clinic days 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 and until the pre-

dose ECG has been performed. Patients should not take their dose until instructed to do so by the Investigator/Study Nurse.

The doses should be taken approximately 12 hours apart for example at 08:00 and 20:00 or 09:00 and 21:00 at the same time points each day. On PK dosing days (i.e. Days 1 & 22), the morning dose 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. On docetaxel dosing days there is no need to alter the time points at which selumetinib is taken. Wherever possible, doses should not be missed. If a patient misses taking a scheduled dose, window ± 2 hours, 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/placebo 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.

Any deviations from dosing schedule, dose interruptions, dose reductions and dose adjustments should be recorded in the eCRF. This includes details of vomiting after taking study medication e.g. date & time of vomiting in relation to dosing.

Patients are permitted to continue to receive selumetinib, following the end of the study (as defined in Section 9.5) if, in the opinion of the investigator, they are continuing to derive clinical benefit, in the absence of significant toxicity. At the end of the study any such patients will be unblinded and if found to be receiving active drug they can begin open label selumetinib. Patients will be dispensed bottles of open label selumetinib 25 mg capsules and will be instructed to take three capsules twice daily (or permanently reduced/adjusted dose if applicable). Patients will continue to receive open label selumetinib as long as they wish to remain on treatment, and they are benefiting from treatment in the opinion of the investigator, and they do not meet the criteria for discontinuation of study treatment (see Section 5.8).

AstraZeneca will continue to supply selumetinib after completion of this study until either selumetinib is licensed in that country, or it is determined that the benefit to risk profile does not support continued development of selumetinib, or the national health authority has deemed the drug not approvable. In all these scenarios, AstraZeneca will work with investigators on the proper transition of patients to alternative therapies if possible.

5.5.3 Additional study drug

5.5.3.1 Docetaxel

Docetaxel 75 mg/m^2 will be administered intravenously on Day 1 of every 21-day cycle. It is anticipated that patients receive up to 6 cycles of docetaxel, in the absence of significant toxicity. Investigators may decide to reduce the number of cycles of docetaxel if significant toxicity develops. Further cycles of docetaxel may also be administered at the investigator's discretion if they feel it to be beneficial and it does not contravene local practice.

Docetaxel will be sourced as marketed commercially available material/locally sourced or prescribed in accordance with the local prescribing information.

Pre-treatment may be administered as per local practice e.g. an oral corticosteroid, such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can be used.

Dose reductions to be performed as per Section 5.5.6. Any deviations from dosing schedule, dose interruptions, or dose reductions should be recorded in the eCRF.

5.5.3.2 Pegylated G-CSF

Pegfilgrastim 6mg will be administered subcutaneously as a single injection following every administration of docetaxel. Pegfilgrastim should be administered at a minimum of 24 hours after the administration of docetaxel and not within 14 days prior to the next docetaxel administration.

Pegfilgrastim should not be administered in treatment cycles that do not contain docetaxel.

Pegfilgrastim will be sourced as marketed commercially available material/locally sourced where possible or prescribed in accordance with the local prescribing information.

5.5.4 Labelling

Each bottle of selumetinib and matching placebo capsules will be labelled by Pharmaceutical Development Supply Chain, AstraZeneca or designee.

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

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

Information on the bottle labels for open label selumetinib (only supplied following end of study [see Section 9.5]) will include the study code, 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 and dispensing date.

Open label bottles of selumetinib will also have a tear-off portion that will be removed at the time of dispensing and attached to the Patient Drug Accountability Log.

Docetaxel and G-CSF will be supplied and labeled locally in accordance with local procedures if applicable.

5.5.5 Storage

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.

5.5.6 Management of toxicity of study treatment

The immediate management of any adverse event 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.

5.5.6.1 Selumetinib/placebo toxicity management and dose interruption/reduction

Specific guidance for management of adverse events, interruption or reduction of treatment with selumetinib may be considered for particular events (i.e. dyspnoea, rash, stomatitis, diarrhea), as indicated in the algorithms provided in Appendix I "Guidance for Management of Specific Adverse Events in Studies of Selumetinib. Some AEs (hyperphosphatemia and increase in calcium phosphate) should be managed according to local practice.

For all adverse events reported in this study that are considered at least partly due to administration of selumetinib, the following dose reduction/adjustment guidance should be applied:

- Treatment with selumetinib/placebo should be temporarily interrupted if one of the following AEs occurs despite optimal supportive care and is considered related to treatment with selumetinib/placebo:
  - Any intolerable AE regardless of grade
  - Any AE ≥ CTCAE Grade 3 (despite optimal supportive care)
- If the toxicity resolves or reverts to ≤ CTCAE grade 1 (or to CTCAE grade 2 for rash) or baseline within 4 weeks of onset and the patient is showing clinical benefit, selumetinib may be restarted at the same dose or at a reduced dose, at investigator's judgement. The following step-wise dose reductions of selumetinib to 75 mg od, 50 mg bd, 50 mg od, then permanent discontinuation, are recommended.
  - If a further episode of the same AE subsequently requires dose interruption, selumetinib may be restarted at the next dose level down on improvement of the AE

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

- If the toxicity does not resolve to ≤ CTCAE grade 1(or to CTCAE grade 2 for rash) or baseline after 4 weeks, then the selumetinib treatment should be permanently discontinued and the patient observed until resolution of the toxicity.

- Whilst a patient is still on combination therapy selumetinib/placebo should not be re-escalated to an earlier dose level on improvement of an AE. The schedule of assessments described in the Study Plan (Table 3), should continue relative to the randomisation visit in the event of selumetinib/placebo dose interruption or reduction.

- If a patient permanently discontinues docetaxel while receiving a reduced dose of selumetinib/placebo, selumetinib/placebo can then be re-escalated at the investigators discretion and given as monotherapy.

All dose delays, reductions and adjustments will be recorded in the appropriate electronic system i.e. eCRF in RAVE.

5.5.6.2 Docetaxel Dose Reduction

AEs considered related to administration of docetaxel are listed in the docetaxel product information.

In line with the docetaxel prescribing information, treatment with docetaxel should be withheld on occurrence of the following toxicities, if they are considered at least partly due to docetaxel:

- ANC $<0.5 \times 10^9$/L for more than 7 days

- Febrile neutropenia

- Severe (CTCAE grade 3 or 4) or cumulative cutaneous reactions

- Severe (CTCAE grade 3 or 4) non-haematological toxicities.

Therapy with docetaxel can be re-started upon the resolution of the toxicity to CTCAE grade 1 or baseline, and may continue at a permanently reduced dose as per local practice, e.g. 55 mg/m^2.

If patients permanently discontinue selumetinib/placebo treatment while receiving a reduced dose of docetaxel, docetaxel can then be re-escalated again at the investigators discretion if given as monotherapy in subsequent cycles.

Patients must not receive subsequent cycles of docetaxel until ANC recovers to $\geq 1.5 \times 10^9$/L and platelets recover to a level of $\geq 100 \times 10^9$/L.

Patients who develop peripheral neuropathy ≥CTCAE grade 3 should have docetaxel treatment permanently discontinued. Docetaxel should be stopped for an allergic/hypersensitivity reaction ≥ CTCAE grade 3, if clearly related to docetaxel. Further administration of docetaxel should be in accordance with the docetaxel prescribing information.

For further recommendations on the adjustment of docetaxel dose and frequency of administration refer to the docetaxel prescribing information.

5.6 Concomitant and post-study treatment(s)

Information on any treatment from the time of signed ICF and all concomitant treatments given during the study, with reasons for the treatment, will be recorded on the eCRF in the WBDC system (RAVE).

The following treatment/drugs are restricted in this study:

- No other anti-cancer agents or investigational drugs should be administered whilst patients are receiving study medication. The investigator can initiate any subsequent anti-cancer therapy only after the patient has discontinued all study treatment (selumetinib/placebo and docetaxel).

- Selumetinib/placebo capsules contain vitamin E in the form of D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS), a water-soluble form of vitamin E, which acts as a formulation excipient. The maximum daily dose of vitamin E that a study subject may receive from selumetinib/placebo is approximately 261.6mg/day. Therefore:

  – Patients should not take any supplemental vitamin E. High doses of vitamin E have been reported to cause bleeding and interrupt blood coagulation processes.

  – Selumetinib/placebo should be administered with caution in patients who are receiving concomitant coumarin anticoagulant medications, e.g. warfarin. These patients should have their INR monitored / anticoagulant assessments conducted more frequently and the dose of the anticoagulant should be adjusted accordingly.

- 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.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

Patients may receive treatment with corticosteroids while on study treatment. Bisphosphates or other bone targeting agents (e.g. denosumab) for treatment of bone metastases are permitted during the study.

Following discontinuation from study treatment for any reason patients may receive any subsequent therapy for their disease at the discretion of the investigator. Details of such treatment are to be recorded in the eCRF.

5.7 Treatment compliance

The administration of all study drugs (including investigational products, IP) should be recorded in the appropriate sections of the eCRF.

The patient needs to record the dose and the time of dose intake for the evening dose prior to Visit 5 (per protocol on day 21). This information has to be provided to the site staff. The information will be entered into the database.

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5.7.1 Accountability

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

The study personnel will account for all study drugs dispensed to and returned from the patients.

It is the investigator's/institution's responsibility to establish a system for handling study treatment so as to ensure that:

- Deliveries of such products from AstraZeneca are correctly received by a responsible person (e.g. a pharmacist)
- Deliveries are recorded
- Study treatments are handled and stored safely and properly
- Study treatments are dispensed only to study patients in accordance with the protocol

For IP (selumetinib/placebo), study site personnel or the AstraZeneca monitor will account for all received study drugs and return all unused study drugs to AstraZeneca after the proper accountability done by AstraZeneca monitor. Certificates of delivery and return should be signed.

If IP is destroyed at site then study site personnel or the AstraZeneca monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

For additional study drug (e.g. docetaxel, pegylated G-CSF), study site personnel will account for these additional study drugs locally procured at the site and for appropriate destruction according to local requirements.

5.8 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event (please refer to Section 5.5.6 and Appendix I 'Guidance for Management of Specific Adverse Events in Studies of Selumetinib')
- Severe non-compliance to study protocol as judged by the Investigator and/or AstraZeneca
- Risk to patients as judged by the investigator or AstraZeneca
- A female patient becoming pregnant
- Condition under investigation worsened
- Objective disease progression, based on RECIST 1.1 evaluation
- Patients incorrectly initiated on study medication (Section 5.3)

Patients who have completed 6 cycles of docetaxel should continue on selumetinib/placebo until objective disease progression according to RECIST 1.1. Further cycles of docetaxel can be given if the investigator feels it to be beneficial and it does not contravene local practice.

5.8.1 Procedures for discontinuation of a patient from study treatment

A patient that decides to discontinue study treatment (selumetinib/placebo or docetaxel) will always be asked about the reason(s) for discontinuation from study treatment and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); LCSS, SF-36 v2 should be completed, and all study drugs should be returned by the patient. These patients should continue to be followed for PFS and OS, where applicable, unless the patient withdraws consent from these assessments and/or the study (See Section 5.9).

See Section 3.1.6 for procedures for discontinuation from study treatment.

5.9 Withdrawal from study

Patients are at any time free to withdraw from 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 and assessed by an investigator. Adverse events will be followed up (see Sections 6.4.3 and 6.4.4); questionnaires (e.g. for patient reported outcomes) and all study drugs should be returned by the patient.

Withdrawn patients will not be replaced.

Reasons for withdrawal from the study:

- Eligibility Criteria Not Fulfilled
- Death
- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment. In this event, the patient will be specifically asked if they are withdrawing consent to: -
  - further participation in the study including any further follow up (e.g., survival calls)
  - withdrawal of consent to the use of their study generated data
  - withdrawal to the use of any samples (see Section 7.5)

If a patient wishes to withdraw their consent to further participation in the study, including survival follow-up (which could be conducted by telephone) this should be clearly documented in the patient notes and in the clinical study database.

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

See Appendix D for details of withdrawal of optional genetic research.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The RAVE WBDC system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRF. A copy of the completed eCRF s will be archived at the study site.

6.2 Data collection at enrolment and follow-up

A study initiation visit must be conducted at the centre prior to the commencement of any study activities requiring informed consent. A schedule for the tests and evaluations to be conducted in this study is contained in this section and in the study plan Table 3.

See Table 3 and refer to Section 3.1 for details on procedures/assessments required at all time points throughout the study.

6.3 Efficacy

6.3.1 RECIST 1.1 Investigator Assessment

The radiological examinations performed in the conduct of this study should be retained at site as source data and be available for collection by the sponsor for centralised review.

RECIST 1.1 criteria will be used to assess each patient's tumour response to treatment and allow calculation of PFS, ORR and DoR. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria [CR (complete response), PR (partial response), SD (stable disease) or PD (progression of disease)] are presented in Appendix J. See Section 3.1 for considerations related to RECIST 1.1 assessments

The methods used at baseline for assessment of tumour burden [CT or MRI scans of chest and abdomen (including liver and adrenal glands)] must be used at each subsequent follow-up assessment. Any other areas of disease involvement should be additionally investigated based on the signs and symptoms of individual patients.

If the investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesions (NTLs) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient’s status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

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

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

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

6.3.2 RECIST 1.1 Blinded Independent Central Review (BICR) Assessment

A planned BICR of a random sample of scans, from approximately 200 evaluable patients (with both progressive and non-progressive disease by investigator assessment), used in the assessment of tumours using RECIST 1.1 will be conducted. However imaging assessments for all patients will be collected in case BICR of additional patients is required at a later date. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed CRO to enable central analysis. Results of this independent review will not be communicated to Investigators and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the Investigator. A concordance analysis will be conducted to identify any potential biases in the investigator assessments compared with BICR according to RECIST 1.1 (see Section 12.2.3). If any potential biases are identified, a BICR of additional patient scans may be performed.

6.4 Safety

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.

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

6.4.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period. The follow up period is defined as 30 days ±7 days after last dose of study treatment.

SAEs will be recorded from the time of informed consent. Patients who discontinue study treatment for reasons other than disease progression, and are continuing to have RECIST assessments, following the 30 days after the last dose of the last study treatment will only have study drug or study procedure related SAEs captured until the patient is considered to have progressive disease.

For patients who continue to receive treatment beyond the defined end of study, investigators will continue to report all SAEs until 30 days after treatment is discontinued.

AEs and SAEs will not be collected for the first-line patients who have only signed consent to the *KRAS* mutation status assessment of archival tumour samples.

Follow-up of unresolved adverse events

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

Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade/changes in CTCAE grade
- Whether the AE is serious or not
- Causality due to selumetinib/placebo (yes or no)
- Action taken with regard to selumetinib/placebo
- Causality due to docetaxel (“yes” or “no”)
- Action taken with regard to docetaxel
- Causality due to G-CSF (“yes” or “no”)
- Treatments in relation to event
- Outcome

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

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

- Causality assessment in relation to Docetaxel
- Causality assessment in relation to selumetinib/placebo
- Causality assessment in relation to G-CSF
- Description of AE

The grading scales found in the revised National Cancer Institute CTCAE version 4.03 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

AEs will be coded using MedDRA (Medical Dictionary for Regulatory Activities).

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.

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.

Causality collection

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

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

A guide to the interpretation of the causality question is found in Appendix B to the 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 CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

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

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

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 E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

All events of neutropenia CTCAE 3 and 4 should be recorded as AE or SAE if serious criteria are met also if not associated with clinical signs or symptoms.

All events of neutropenia, regardless of grade, for which supportive G-CSF therapy is administered, should be reported as Adverse Event or Serious Adverse Even if serious criteria are met.

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, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.4.4 Reporting of serious adverse events

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

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

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the 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/listedness is the Investigator Brochure (IB) selumetinib and the European Union (EU) Summary of Product Characteristics (SPC) docetaxel.

6.4.5 Procedures and Safety Management

For further details on the study plan and all procedures see Section 3.

6.4.5.1 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.

If an abnormal ECG finding at the screening assessment is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. During the study, clinically significant abnormal ECG findings not present at baseline should be reported as an AE. If present, the clinical signs and symptoms associated with the abnormal finding should be reported as the AE with the ECG abnormality given as explanatory information.

At the randomisation visit (Visit 2 Day 1) patients will have a single 12-lead ECG taken before first dose of selumetinib. The assessment is not required if taken within 14 days of the screening ECG and the patient's condition has not changed (no new treatment during this period of time with no new complication or aggravation).

Single ECGs should be performed at the time of significant LVEF drop (Section 3.1.5) 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.

6.4.5.2 Vital Signs

Vital sign assessments, including weight, will be performed as per the study plan (see Table 3) and at the time of any echocardiogram/MUGA assessment. Additionally at the discretion of the investigator if clinically indicated. These assessments should not be repeated during the relevant visit if already performed as part of the echocardiogram/MUGA procedure.

Temperature should be recorded in the case of febrile neutropenia/ neutropenia (CTCAE grade 3 or 4) and as clinically indicated.

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

6.4.5.3 Ophthalmologic examination

An ophthalmologic examination (best corrected visual acuity, intraocular pressure and slit lamp fundoscopy) should be performed at screening.

If a patient experiences AE/symptoms of visual disturbance (including blurring of vision) a complete ophthalmological examination, including a slit-lamp examination, must be performed. If an abnormality is detected, fundus photography and an OCT scan can also be performed where required. AEs are to be managed accordingly to Appendix I, 'Guidance for Management of Specific Adverse Events in Studies of Selumetinib'.

If retinal abnormality prior to or at time of selumetinib discontinuation has been observed a repeat ophthalmological examination is to be performed 30 days after discontinuation of selumetinib in order to document reversibility.

6.4.5.4 Echocardiogram or MUGA

An echocardiogram will be conducted at screening (up to 28 days prior to randomisation) 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.

Echocardiography/MUGA will also be carried out if a patient develops signs and/or symptoms suggestive of deterioration in left ventricular function/cardiac event.

Patients who had a drop in LVEF (decrease by > or equal to 10 percentage points and to an absolute value < 55%) prior to or at time of discontinuation of selumetinib/placebo should, where possible, have a follow up echocardiogram (single ECG) and vital signs (including weight) performed 30 days after permanent discontinuation of selumetinib/placebo in order to document reversibility.

Patients experiencing an asymptomatic but clinically significant drop in LVEF (decrease by > or equal to 10 percentage points and to an absolute value < 55%) should be managed according to the algorithm provided in Appendix I 'Guidance for Management of Specific Adverse Events in Studies of Selumetinib'.

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.

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

6.4.5.5 Laboratory safety assessment

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

The following laboratory variables will be measured:

Table 4 Laboratory safety assessments

Clinical chemistry	Haematology	Urinalysis (Dipstick)
S/P - Albumin	B - Erythrocyte count	U - Glucose
S/P - ALT	B - Haemoglobin	U - Protein
S/P - AST	B - Platelet count	U - Blood
S/P - ALP	B - Leucocyte cell count	
S/P - Total Calcium	B - Leucocyte differential count (absolute count):	
S/P - Creatinine	B - Neutrophils	

Table 4 Laboratory safety assessments

Clinical chemistry	Haematology	Urinalysis (Dipstick)
S/P - Gamma glutamyl transferase (γGT)	B - Eosinophils	
S/P - Magnesium	B - Basophils	
S/P - Phosphate	B - Lymphocytes	
S/P - Potassium	B - Monocytes	
S/P - Sodium		
S/P - Total protein		
S/P - Total bilirubin		
S/P - Urea nitrogen		
B - INR*		
S/P – CPK**		
S/P - Troponin (isoform as per institutional norm)***		

S – Serum P - Plasma B – Blood U - Urine

* For patients receiving warfarin (coumarin derivates), INR monitoring should be conducted and recorded in the eCRF

** CPK to be assessed at screening and if clinically indicated (e.g. muscle symptoms). See Section 3.1.4.

*** Troponin (I/T - isoform as per institution norm) should be assessed at screening, on occurrence of significant LVEF drop (≥ 10 percentage points from baseline and an absolute value < 55%) or any cardiorespiratory events with no obvious diagnosis. If troponin not available as per local practice, creatinine kinase – MB (CK-MB) should be assessed

Clinical chemistry, haematology and urinalyses 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/placebo should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 30 days (±7days) after permanent discontinuation of selumetinib/placebo.

NB. In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix E ‘Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy’s Law’, for further instructions.

Urinalysis (dipstick) to be performed at screening, before docetaxel administration at cycles 2 & 3 (week 3 & 6) and to be repeated as clinically indicated. Urine microscopy to be assessed if other urinalysis measurements are abnormal/if clinically indicated

For blood volume see Section 7.1.

During docetaxel dosing, samples may be collected up to 2 days prior to administration of chemotherapy. Additional samples may be collected if clinically indicated at the discretion of the investigator. Date, time and result will be captured on the eCRF.

6.5 Patient reported outcomes (PRO)

6.5.1 Lung Cancer Symptom Scale (LCSS)

Disease-related symptoms will be assessed using the LCSS. The LCSS was developed specifically for use in lung cancer studies and has been shown to be valid, reliable and responsive to changes in underlying lung cancer (Burke et al, 1985; Monras et al, 1985; Hollen et al, 1994). It evaluates six major symptoms associated with lung malignancies and their effect on overall symptomatic distress, functional activities, and global quality of life. It captures the symptoms most likely to be influenced by therapeutic interventions.

The LCSS includes nine visual analogue scales (VAS) and has a recall period of 'the past day', which has been operationalized as the past 24 hours. Six of the nine items address major symptoms of lung cancer and constitute the ASBI; loss of appetite, fatigue, cough, dyspnoea, haemoptysis, and pain, while the remaining three VAS are summary items which assess symptom distress, interference with activity levels, and global quality of life. The interval level VAS version uses 100 mm lines to measure the intensity for each item. Each item is given a score equal to the length of the line marked by the patient with scores ranging from 0-100, and with 0 = the best possible status, and 100 = to the worst possible status. The ASBI and the summary score are calculated from a mean of the items included in each score.

Seven of the items have the anchors 'none'/'not at all' and 'as much as it could be'/'as bad as it could be'. The appetite item ranges from 'as good as it could be' to 'as bad as it could be' and the global HRQoL item ranges from 'very high' to 'very low'. The patient is asked to focus on describing lung cancer symptoms. Initial administration time is 8 minutes, including instructions, which generally decreases to 3-5 minutes with repeated administrations.

Adequate psychometric properties have been demonstrated including internal consistency reliability, test-retest reliability, construct validity (multi-trait, multi-method approach) and criterion validity (Hollen et al, 1994). The LCSS will be completed before any study related assessments at the time points listed in Table 3.

If a patient discontinues study treatment for reasons other than objective disease progression, LCSS is to be completed in line with the RECIST 1.1 assessment schedule until objective disease progression (regardless of whether the subject withdraws from randomised therapy or receives another anti-cancer therapy prior to progression) and the LCSS should be administered at the discontinuation visit for PD and one additional assessment should be completed 30 days following the discontinuation visit for objective disease progression.

6.5.2 SF-36v2

The Medical Outcomes Study 36-item short form health survey (SF-36v2) is included for the purpose of assessing HRQoL in both the selumetinib and placebo treatment groups. The SF-36v2 is the most widely used generic measure of HRQoL/health status, and commonly used as an endpoint in clinical trials conducted in a variety of health conditions (Ware et al 1992; Ware et al 1993; McHorney et al, 1993; McHorney et al, 1994).

It assesses HRQoL/health status through a profile eight scales: physical functioning (10 items), role limitations due to physical health problems (4 items), bodily pain (2 items), social functioning (2 items), general mental health (5 items), role limitations due to emotional problems (3 items), vitality, energy or fatigue (4 items) and general health (5 items). Selection of the items was informed by the relevant literature as well as a review of existing instruments (Ware et al 1993). In addition, psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores and a preference-based health utility index (the SF-6D) can also be calculated. Both the summary scores and the domain scores have well-established evidence of validity and reliability across diverse patient groups (McHorney et al, 1993; McHorney et al, 1994).

SF-36v2 is a generic measure, which has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. To that end, age-specific SF-36v2 norms have been established in the general population and in a number of common health conditions such as hypertension and depression. These norms allow comparison of SF-36v2 scores generated in trials against age-based norms in the general population or in reference populations for the disease. In addition, the SF-36 has previously been used in NSCLC trials (e.g. Sarna et al, 2002; Moinpour et al, 2008).

The SF-36v2 has a 1-week recall period. The SF-36v2 will be completed after the LCSS but before any study related assessments at the time points listed in Table 3 (i.e. baseline, cycle 3, cycle 5, objective disease progression and 30 days post-progression).

If patient discontinues study treatment for reasons other than objective disease progression, SF-36v2 is to be completed at the time of objective disease progression (regardless of whether the subject has received another anti-cancer therapy prior to progression) and again approximately 30 days later.

The SF-36 v2 will be used to explore the impact of treatment and disease state on health state utility. This exploratory analysis will primarily be used to support future economic evaluations of selumetinib.

6.5.3 Administration of PRO questionnaires

Patients will complete the PRO questionnaires on paper at the clinical site. Relevant training of the study staff to administer the questionnaires will be provided before study start.

Each centre must designate responsibility for the administration and compliance monitoring of the questionnaires to a specific individual (e.g. a research nurse). An individual who will serve as a back up should also be designated. It is important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection. The time of completion of each questionnaire will be recorded by the site staff. Instructions for completion of the questionnaires are as follows:

Following informed consent and randomisation, questionnaires must be completed by the patient before any investigations and before discussions about their disease with the clinic staff.

Patients should be provided with a suitable, private place to complete the questionnaires alone (i.e. without assistance from clinic staff, relative or friend). If a patient asks site staff for assistance the staff should respond that the patient should answer using their best judgement or leave the question blank. If a patient is unsure how to choose between two adjacent responses they should be directed to choose the more severe response. If possible, patients should be reminded to bring reading glasses to the clinic prior to the visit. The patient should be given sufficient time to complete at their own speed.

If a patient is unable to complete the questionnaires unaided, the designated clinic staff member will read the questions verbatim to the patient and record the answers, without interpretation. Where significant assistance in completing the questionnaires is required, this must be recorded.

Any reason for non-completion of the questionnaires should be recorded in the patient's medical records.

It is important that the patient can speak and understand the language of the provided questionnaire to be able to answer the questions by themselves.

6.6 Pharmacokinetics

6.6.1 Collection of samples

Venous blood samples (2mL) for determination of plasma concentrations of selumetinib and N-desmethyl selumetinib will be taken as outlined in Table 3 at the timepoints detailed below, taking the first selumetinib/placebo dose of the day as the reference point (other selumetinib metabolites [e.g. selumetinib amide] may also be determined):

- Pre-dose
- Between 0.5 and 2 hours post-dose
- Between 2.5 and 4.5 hours post-dose
- Between 6 and 8 hours post-dose

On pharmacokinetic (PK) sampling days, docetaxel dosing should not occur until the pre-dose PK samples have been taken. The second dose of selumetinib should be taken after the last PK samples have been taken on that day and approximately 12 hours after the first dose.

The actual sample date and time of all PK samples must be recorded in the eCRF.

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

For blood volume see Section 7.1.

6.6.2 Determination of drug concentration

Samples for determination of selumetinib and N-desmethyl selumetinib concentrations in plasma will be analysed by on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Other selumetinib metabolite concentrations may also be measured e.g. selumetinib amide.

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 and its metabolites) at the time of receipt by the bioanalytical laboratory will be analysed.

For each placebo subject, samples will only be analysed on a 'for cause' basis, e.g. if no quantifiable concentrations were observed in a subject's samples when the drug was expected to be present.

Results will be only reported for samples shipped within a timeframe for which the stability of selumetinib and N-desmethyl selumetinib (and potentially other selumetinib metabolites) in the samples has been validated and shown to be acceptable.

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics (optional)

6.8.1 Collection of pharmacogenetic samples

A single blood sample will be obtained from consenting patients either at Visit 2 or after randomisation.

See appendix D ('Pharmacogenetics Research') for further details.

For blood volume see Section 7.1.

6.9 Biomarker Analysis

6.9.1 Tumour Assessment of *KRAS* Mutation Status

See Section 3.1.9.1and Figure 3 for details.

On completion of the central *KRAS* mutation testing, any remaining tissue sample or slides will be stored for potential retrospective biomarker analysis. If requested tumour blocks will be repatriated.

6.9.2 Mandatory collection of plasma for exploratory analysis of cfDNA

All randomised patients will provide a plasma samples for the extraction and analysis of cfDNA. Analysis of *KRAS* mutation status will be assessed on the cfDNA samples to assess the correlation between tumour versus plasma based mutation analysis.

This is an exploratory analysis with the aim of developing less invasive methodologies for the analysis of tumour mutation status. Data generated from this analysis will not be used to aid patient recruitment in this study.

Samples will be collected prior to randomisation and at treatment discontinuation (selumetinib/placebo and docetaxel):

- 10 mL blood sample for preparation of plasma

Samples will be collected, labelled, stored and shipped as detailed in the laboratory manual.

Residual material will be used for exploratory biomarker research (e.g., phosphatase and tensin homolog [PTEN] mutation status).

6.10 Health economics

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

- Hospital episodes including type of contact (hospitalisations, outpatient, day case), reason, length of stay (including ICU) and concomitant medications, procedures and test undertaken

- Treatment related to adverse events

The above resource use data will be captured using RAVE.

The economic evaluation of selumetinib will also require an assessment of health state utility. This will be derived from the SF-36v2 and further details are provided under relevant patient reported outcomes section of the protocol

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 5 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)*	No. of samples	Total volume (mL)
Safety	Clinical chemistry	10	8	80
	Haematology	4	8	32
Pharmacokinetic		2	8	16
Plasma sample for cfDNA		10	2	20
Genetics (optional)		10	1	10
Total			27	158

* Approximate volumes

The total volumes of blood given in Table 5 are based upon a patient remaining in the study for 3 months.

After week 12, blood samples will be taken for clinical chemistry and haematology every 3 weeks until discontinuation. In addition, on occurrence of all cardio respiratory AEs with no obvious diagnosis or a significant drop in LVEF, a 4 mL blood sample will be taken to assess Troponin (isoform as per institutional norm).

Clinical chemistry and haematology samples are analysed locally, therefore volumes may vary according to local practice.

7.2 Handling, storage and destruction of biological samples

After analyses have been completed, any remaining biological samples will be disposed of or retained for further research use, as described here.

Biological samples for future research will be retained at AstraZeneca R&D site or CRO, on behalf of AstraZeneca, for a maximum of 15 years following the Clinical Study Report. The results from future analysis will not be reported in the Clinical Study Report but separately in the bioanalytical method validation report.

7.2.1 Pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. Pharmacokinetic samples may be disposed of or destroyed and

anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR. Anonymised samples will be retained for no more than 5 years after the CSR is finalised.

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

7.2.2 Optional Pharmacogenetic samples

For details concerning the coding and storage of genetic samples please refer to Appendix D 'Pharmacogenetics Research'.

7.2.3 Clinical chemistry, haematology and urinalysis samples

All clinical chemistry, haematology and urinalysis samples will be analysed by the local laboratory and will be handled according to local laboratory practice.

The analyte stability limits defined by the local laboratory will be applied to all analyses performed for this study. Samples that fall outside these stability limits should not be analysed. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits.

7.2.4 Mandatory tumour sample for *KRAS* mutation assessment

A tissue section and a DNA aliquot will be retained for potential regulatory follow up (including samples from screen failures).

Residual material will be retained for the analysis of other biomarkers.

Where required, rapid repatriation of samples can be requested.

7.2.5 Mandatory plasma sample for exploratory analysis of cfDNA

Residual material will be retained for the analysis of other biomarkers.

7.3 Labelling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

The Principal Investigator at each 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.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is sooner.

7.5 Withdrawal of informed consent for donated biological samples

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

Tumour sample for assessment of *KRAS* mutation status: As collection of the biological sample is an integral part of the study, then the patient is withdrawn from further study participation.

cfDNA sample: Although mandatory, the patient may continue on the study if the patient has already randomised.

Genetic sample: Patients may withdraw for genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment.

The Principal Investigator:

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

- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/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 and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Patient data protection

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

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

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

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

8.3 Ethics and regulatory review

An Institutional Review Board (IRB) / Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable IRB / Ethics Committee, and to the study site staff.

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

The IRB / 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 IRB / Ethics Committee annually.

Before enrolment of any patient into the study, the final 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, IRBs / Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

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

8.4 Informed consent

The PI at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study

- Ensure each patient is notified that they are free to discontinue from the study at any time

- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICFs are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

8.5 Changes to the protocol and informed consent form

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

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

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

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

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

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 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.

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC and IVRS/IWRS systems.

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

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

Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and host genetic research with AstraZeneca personnel or delegate. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the patients' samples will also be made clear.

9.3 Monitoring of the study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual, that study drug accountability checks are being performed and that PRO questionnaires are being completed by patients

- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g. clinic charts)

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

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

9.3.1 Source data

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

9.4 Study agreements

The PI 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 terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

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

9.4.1 Archiving of study documents

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

9.5 Study timetable and end of study

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

The study is expected to start in Q4 2013 and to end by Q1 2017.

The primary analysis will occur following approximately 325 death events. At this time point, the clinical study database will lock for primary analysis, data analysis will be performed and a CSR written. Patients are however permitted to continue to receive study treatment beyond the database lock if, in the opinion of the investigator, they are continuing to receive benefit from treatment with selumetinib/placebo or docetaxel (see Section 5.5.2). For patients who do

continue to receive treatment beyond the time of this data cut-off, investigators will continue to report all SAEs to AstraZeneca Patient Safety until 30 days after study treatment is discontinued, in accordance with Section 6.4.4 (Reporting of Serious Adverse Events). Additionally as stated in Section 6.4.3 (Recording of adverse events), any SAE or non-serious adverse event that is ongoing at the time of this data cut-off must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

Under certain circumstances, and based on the guidance from the IDMC, patients currently receiving placebo may be offered selumetinib.

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

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by AstraZeneca Data Management Centre staff.

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

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

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

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

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

The *KRAS* mutation status of the patient's tumour sample will not be recorded in the eCRF by the central laboratory, but will be transferred to Cognizant as an electronic file. The *KRAS* mutation status will be provided to investigators by the central laboratory as part of the screening process, prior to a patient being randomised.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 RECIST 1.1 based endpoints

All RECIST assessments, whether scheduled or unscheduled will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anti-cancer therapy.

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.

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

For TLs:

Progressive disease is defined as a ≥ 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters since treatment started.

Complete response is defined as the disappearance of all TLs. Any pathological lymph nodes selected as a TL must have a reduction in short axis to < 10mm.

Partial response is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters as long as criteria for PD are not met.

Stable disease is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

11.1.2 Progression Free Survival (PFS)

The primary endpoint is PFS (defined by RECIST 1.1 as assessed by the investigator).

PFS is defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the subject progresses or dies after two or more missed visits, the subject will be censored at the time of the latest evaluable RECIST1.1 assessment. If the subject has no evaluable visits or does not have baseline data they will be censored at day -0 unless they die within two visits of baseline.

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

RECIST 1.1 assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression

- When censoring a subject for PFS the subject will be censored at the latest of the dates contributing to a particular overall visit assessment

11.1.3 Overall Survival

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

Note, survival calls will be made in the two weeks following the date of DCO for the analysis, and if patients are confirmed to be alive (if the death date is post the DCO date) these patients will be censored in the analyses as of the date of DCO.

11.1.4 Objective Response Rate

ORR rate is defined as the number (%) of subjects with at least one visit response of CR or PR. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR.. For patients who receive a subsequent therapy, the tumour assessments performed after the start of the subsequent therapy will not be included in the calculation of ORR. As measurable disease is an inclusion criterion for the study, the denominator for ORR will be a all randomised subjects.

11.1.5 Duration of Response

Duration of response will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

If a subject does not progress following a response, then their duration of response will be censored at the PFS censoring time.

Duration of response will not be defined for those subjects who do not have documented response.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Adverse events (AE)

Data from all cycles of randomised treatment will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient and treatment group. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial treatment group.

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

Any AE occurring within 30 days of study treatment discontinuation (i.e., the last dose of selumetinib/placebo) will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study medication) will be flagged in the data listings.

A separate data listing of AEs occurring more than 30 days after discontinuation of selumetinib/placebo will be produced. These events will not be included in AE summaries. Note, this includes adverse events that occur during treatment with docetaxel, if selumetinib/placebo was discontinued first but docetaxel treatment continued.

11.2.2 Other significant adverse events (OAE)

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 DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

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

11.2.3 Safety Assessments

For change from baseline summaries for vital signs, laboratory data, ECGs, echocardiogram/MUGA, physical and ophthalmological examination, the baseline value will be the latest result obtained prior to the start of study treatment.

QTcF (Fridericia) will be derived during creation of the reporting database using the reported ECG values (RR and QT).

QTcF = QT / RR^ (1/3) where RR is in seconds

Corrected Calcium and Calcium Phosphate product will be derived during creation of the reporting database using the following formulas:

Corrected Calcium (mmol/L) = Total Calcium (mmol/L) + ([40 – Albumin (G/L)] x 0.02)

Calcium Phosphate (mmol/L) = Corrected Calcium (mmol/L) x Phosphate (mmol/L).

The denominator used in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality. For example:

If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded

If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post dose-value recorded

The denominator in vital signs data should include only those patients with recorded data.

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 Lung Cancer Symptom Scale (LCSS)

Patient-reported symptoms will be assessed using the ASBI, which is a sub-score of the LCSS. The ASBI score is derived from the mean of the scores from the six individual symptom questions of the LCSS (loss of appetite, fatigue, cough, dyspnoea, haemoptysis and pain) in accordance with the recommendations of the developers. Each question is scored from 0-100 on a VAS with a higher score indicating greater symptom burden.

11.3.1.1 Time to symptom progression

Symptom changes will be determined based on changes in the ASBI score compared to baseline, with a minimum clinically meaningful change in symptoms defined as a change in the ASBI score of ≥10 (Hollen and Gralla 2000; Sarna et al 2008).

The ASBI is considered to target the most relevant and important symptoms and time to symptom progression (TSP) will be assessed through evaluation of the change in ASBI between baseline and later time points. TSP will be defined as the time from randomisation until the date of first clinically meaningful symptom deterioration (an increase in the ASBI from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, provided death occurs within two LCSS assessment visits of the last LCSS assessment where ASBI could be evaluated, and regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to symptom deterioration.

Patients whose symptoms (as measured by ASBI) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last LCSS assessment where ASBI could be evaluated. Also, if symptoms progress after two or more missed LCSS assessment visits or the patient dies after two or more missed LCSS assessment visits, the patient will be censored at the time of the last LCSS assessment where ASBI could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at day 0. The population for analysis of TSP will include a subset of the ITT population who have baseline ASBI scores ≤ 90.

11.3.1.2 Symptom Improvement rate

A clinically meaningful improvement in symptoms will be defined as a decrease in the ASBI from baseline of ≥10.

The symptom improvement rate will be defined as the number (%) of patients with two consecutive assessments at least 18 days apart (i.e. 21 days allowing a visit window of 3 days) which showed a clinically meaningful improvement in symptoms from baseline, the denominator consisting of a subset of the ITT population who have baseline ASBI scores ≥10.

11.3.1.3 Individual items of the LCSS

The 6-symptom items loss of appetite, fatigue, cough, dyspnoea, haemoptysis and pain and the symptom distress and interference with activity levels will be analysed descriptively.

11.3.2 Short-Form Health Survey (SF-36v2)

Patient-reported HRQoL will be assessed using the SF-36v2 questionnaire. It assesses HRQoL/health status using multi-item scales to measure the following eight dimensions: physical functioning; role limitations due to physical health problems; bodily pain; social functioning; general mental health; role limitations due to emotional problems; vitality, energy or fatigue; general health perceptions. In addition to the eight domain scores, two summary scores can also be calculated: the PCS and MCS. Both the summary scores and the domain scores have well established evidence of validity and reliability across diverse patient groups (McHorney et al, 1993; McHorney et al, 1994).

The scores will be derived in accordance with the SF-36v2 manual and interpretation guide. The SF-36v2 scale scores are scored so that a higher score indicates better health and are based on the sum of the items included in a given scale, transformed to a 0-100 scale. The following items are negatively stated and need to be reverse scored: items 1, 6, 8 (if both 7 and 8 are answered), 9a, 9d, 9e, 9h, 11b, 11d. Items 1, 7 and 8 also need to be recalibrated (weighted) as per the instructions of the developers in the manual.

11.3.2.1 Health domain scales and Physical and mental component summary scores

The items included in each scale are as follows:

- PF: Physical functioning - Question 3 (3a-3j)

- RP: Role limitations due to physical health problems – Question 4 (4a-4d)
- BP: Bodily pain – Questions 7 and 8
- SF: Social functioning – Questions 6 and 10
- MH: General mental health – Question 9 (9b, 9c, 9d, 9f, 9h)
- RE: Role limitations due to emotional problems – Question 5 (5a-5c)
- VT: Vitality, energy or fatigue – Question 9 (9a, 9e, 9g, 9i)
- GH: General health – Question 1 and 11 (11a-11d)

The two summary scores PCS and MCS will also be calculated in accordance with the SF-36v2 manual. The SF-36 v2 individual domains and the 2 sub categories will be analysed descriptively.

11.3.2.2 Health state utility derivation

Preference based health status utility values are often used in economic evaluations to estimate the health benefit of treatments. These utility values will be derived from the SF-36v2 non-preference based generic PRO instrument. Two approaches will be used to generate utility values:

- Reduce the SF-36v2 to the SF-6D and apply an algorithm to derive utility value (Brazier et al. 2002)
- Mapping from the SF-36v2 to the EQ-5D using a model specification as outlined in Rowen et al. 2009

The evaluable population will comprise all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of treatment actually received.

11.4 Calculation or derivation of pharmacokinetic variables

The final PK analyses will be the responsibility of Clinical Pharmacology Science, Alderley Park, AstraZeneca, UK.

The plasma concentration-time data for selumetinib and N-Desmethyl selumetinib will be analysed by mixed effects modelling. The aim is to evaluate the pharmacokinetic characteristics of selumetinib and N-Desmethyl Selumetinib including estimating pharmacokinetic variables and quantifying variability. An attempt may be made to identify potentially important covariates such as weight, age, sex and/or concomitant medications. The relationships between plasma exposure and pharmacodynamic parameters (efficacy and

safety) will be explored. Initially graphical representation of the data will be performed but mixed effects modelling of the data may be carried out if feasible.

Other metabolites of selumetinib (e.g. selumetinib amide) may also be analysed as described above.

A detailed pharmacokinetic analysis plan will be provided prior to database lock. Plasma concentration data will be listed for each patient per dose and dosing day but will not be summarised. The analysis will be reported in a separate pharmacokinetic report.

11.5 Calculation or derivation of pharmacodynamic variable(s) (Not applicable)

11.6 Calculation or derivation of pharmacogenetic variables (Not applicable)

11.7 Calculation or derivation of health economic variables

Frequency and estimates of healthcare resource use, including hospital episodes, type of contact (hospitalisation, outpatient, day case), reason, length of stay (including ICU), concomitant medication and procedures and tests undertaken will be derived from the resource use information. The evaluable population will comprise all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received.

11.8 Calculation or derivation of biomarker variables

11.8.1 *KRAS* mutation assessment of tumour sample

Tumour samples will be analysed for mutations of *KRAS* using cobas® *KRAS* Mutation Test and other appropriate techniques as required.

11.8.2 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.

11.8.3 Further biomarker research analysis

Any residual tissue/plasma or DNA remaining from these samples after mutation analysis may be analysed for factors that may influence development of NSCLC 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.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

12.1 Description of analysis sets

See Table 6.

12.1.1 Efficacy analysis set

Intention to treat (ITT): The primary statistical analysis of the efficacy of selumetinib in combination with docetaxel vs placebo in combination with docetaxel will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Note, this is also known as the Full Analysis Set (FAS).

12.1.2 Safety analysis set

All patients who received at least one dose of randomised investigational product, selumetinib/placebo will be included in the safety population. Throughout the safety results sections, erroneously treated patients (e.g., those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group. Treatment received is based on the initial dose of study treatment received, even though patients may have had subsequent dose reductions.

When assessing safety and tolerability, summaries will be produced based on the safety analysis set.

12.1.3 PK Analysis Set

PK data will be analysed according to treatment received. This population will comprise all patients who receive study treatment as per protocol and do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population will be defined by the Study Team Physician, Pharmacokineticist and Statistician prior to any analyses being performed.

Table 6 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
PFS	ITT
OS, ORR, DoR, symptom endpoints, HRQoL	ITT
Demography	ITT
Pharmacokinetic data	PK
Safety Data	

Table 6 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Exposure	Safety
Adverse Events	Safety
Lab measurements	Safety
WHO performance status	ITT
ECHO/MUGA	Safety
Vital Signs	Safety
Ophthalmological examination	Safety

12.2 Methods of statistical analyses

A comprehensive SAP will be prepared before un-blinding of the data.

There will be one treatment comparison of interest:

- Selumetinib 75mg bd in combination with docetaxel 75mg/m^2 vs placebo in combination with docetaxel 75mg/m^2

PFS is the primary endpoint. However, the study has been sized to characterise the OS benefit of selumetinib 75mg in combination with docetaxel. The final analysis of PFS will take place on a pre-specified date when it is predicted that approximately 325 death events have occurred. The exact date will be predicted by modelling the blinded death rate data.

All descriptive statistics will be presented by treatment group. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment group.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of study treatment, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to randomisation.

All data collected will be listed.

Efficacy data will be summarised and analysed on the efficacy (ITT) analysis set.

Safety data will be summarised and analysed on the safety analysis set.

Results of all statistical analysis will be presented using a 95% CI and 2-sided p-value, unless otherwise stated.

The following table details which endpoints are to be subject to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint

Table 7 Formal statistical analyses to be conducted and pre-planned sensitivity analyses

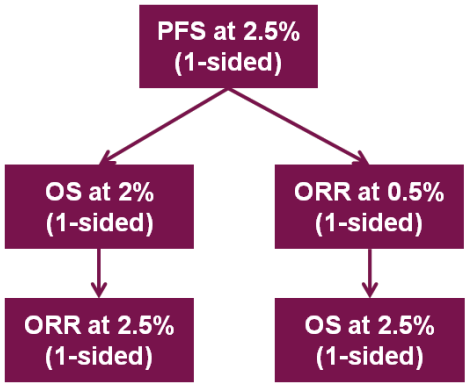
Endpoints Analysed	Notes
PFS	Primary analysis stratified log-rank test using investigator assessment Sensitivity analyses 1) Evaluation Time bias 2) Attrition bias 3) Ascertainment bias Secondary analysis Cox proportional hazards model with covariates
OS	Stratified log-rank test Secondary analysis Cox proportional hazards model with covariates
ORR	Logistic regression using investigator assessment
Time to symptom progression (ASBI)	Stratified log-rank test Sensitivity analyses 1) Attrition bias 2) Analysis where RECIST PD is considered an event *3)* Analysis where censoring at RECIST PD
Symptom improvement rate (ASBI)	Logistic regression

12.2.1 Multiple testing strategy

In order to describe the nature of the benefits of selumetinib treatment, PFS, OS, ORR, time to symptom progression and symptom improvement rate will be tested at a 2-sided significance level of 5%.

However, in order to strongly control the type I error at 2.5% 1-sided, a multiple testing procedure (MTP) with an alpha-exhaustive recycling strategy (Burman et al 2009) will also be employed across the PFS and secondary endpoints OS and ORR. With this approach, the primary endpoint PFS and secondary endpoints OS and ORR will be tested in a pre-defined order as shown in Figure 4 below:

Figure 4 **Multiple testing procedure for controlling type-1 error rate**



The primary endpoint (PFS) is tested at a 1-sided α of 2.5%. If the primary hypothesis of PFS is rejected for superiority, the secondary endpoints will then be tested in the MTP using a weighted proportion of alpha (test mass; the total test mass equals alpha) and test mass becomes available after each rejected hypothesis, which is recycled to secondary endpoints not yet rejected. This testing procedure stops when the entire test mass is allocated to non-rejected endpoints. Implementation of this pre-defined ordered testing procedure, including recycling, will strongly control the Type I error at 2.5% (1 sided) amongst the primary (PFS) and key secondary endpoints.

12.2.2 Progression Free Survival

Progression free survival (PFS) will be analysed using a stratified log-rank test using the Breslow method to handle ties (Breslow, 1974). The stratification factors are WHO Performance Status (0/1) and Histology (squamous/non-squamous). The effect of treatment will be estimated by the HR together with its corresponding 95% CI and p-value. The HR and its CI can be estimated from the log-rank as follows (Berry et al 1991, Collett, 2003, Sellke and Siegmund 1983):

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

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

Where $U = \sum_k U_k = \sum_k \sum_i (d_{1ki}, -e_{1ki})$ is the stratified log-rank test statistic obtained from the SAS LIFETEST procedure, $\sqrt{V} = \sqrt{\sum_k V_k}$, is its standard deviation, k denotes the stratum and d_{1ki} and e_{1ki} are the observed and expected events in group 1, stratum k.

Kaplan-Meier (KM) plots of PFS will be presented by treatment group. Summaries of the number and percentage of subjects experiencing a PFS event, and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each treatment. The proportion of patients alive and progression free at 6 months and 12 months will be summarised (using the

KM curve) and presented by treatment group. These will be presented on a forest plot including the HR and 95% CI from the overall population, and from the sensitivity analyses.

The assumption of proportionality will be assessed. Proportional hazards will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time-periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be is a result of treatment-by-covariate interactions, which will be investigated.

The primary analysis will be based on the programmatically derived PFS based on investigator-recorded assessments.

Subgroup analyses will be conducted comparing PFS between treatments in the subgroups of the full analysis set defined by the stratification factors WHO PS and histology, plus the following factors:

- Gender (Male vs. Female)
- Age at randomisation (< 65 vs. = 65)
- Smoking status (smoker vs. non-smoker (never smoker))
- Status of disease (Locally advanced vs Metastatic)

Other baseline variables may also be included if there is clinical justification or an imbalance is observed across the treatment arms.

The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic factors but from the results observed in Phase II (D1532C00016) it is not expected that these factors will be predictive factors for a qualitatively different treatment effect.

No adjustment to the significance level for testing will be made since all these analyses will be considered supportive of the primary analysis of PFS.

Cox proportional hazards modelling will employed to assess the effect of covariates on the HR estimate. Before embarking on more detailed modelling, an initial model will be constructed, containing treatment and the two stratification factors alone, to ensure any output from the Cox modelling is likely to be consistent with the results of the stratified log-rank test.

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

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% 2-sided level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

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

Additionally, for each subgroup, the HR and 95% CI will be calculated from a single Cox proportional hazards model that contains a term for treatment, the subgroup covariate of interest and the treatment by subgroup interaction term. The treatment effect HR will be obtained for each level of the subgroup from this model. The stratification factors will not be included in the model unless the stratification factor is the subgroup being analysed. The Cox models will be fitted using SAS® PROC PHREG with the Efron method to control ties. TheseHR and 95% CIs will be presented on a forest plot along with the results of the overall primary analysis.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 10 events for each treatment arm in a subgroup), the relationship between that subgroup and PFS will not be formally analysed. In this case, only descriptive summaries will be provided.

12.2.3 Sensitivity Analyses for Primary Endpoint (PFS)

Sensitivity analyses will be performed to assess the possible presence of time-assessment bias (i.e. differential assessment times between treatment groups).

(a) Evaluation-Time bias

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled timepoints. The midpoint between the time of progression and the previous evaluable RECIST assessment will be analysed using a stratified log-rank test. This approach has been shown to be robust to even highly asymmetric assessment schedules (Sun and Chen 2010).

(b) Attrition bias

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

(c) Ascertainment bias

Ascertainment bias will be assessed from carrying out a blinded independent central review. The objective of the BICR is to detect potential evaluation bias in the investigator assessment of PFS. Evaluation bias will be assessed using methods by Dodd (Dodd et al 2011) and Stone (Stone et al 2015). An audit plan will be included in the SAP to outline the criteria for determining when a complete review of scans will be conducted via a central review.

12.2.4 Overall Survival (OS)

OS data will be analysed using the same methodology and models as described in Section 12.2.2 but excluding the global interaction test. The final analysis of OS will be analysed when approximately 325 deaths have occurred (~65% maturity). No further analyses of OS are planned beyond this point unless requested by Health Authorities.

A Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary OS analysis is reversed will be produced to assess whether there is an imbalance in censoring for OS.

12.2.5 Objective response rate (ORR)

The ORR will be based on the investigator's assessment of RECIST. A summary of ORR will be presented by treatment group. ORR will be compared between selumetinib in combination with docetaxel vs. placebo in combination with docetaxel using an adjusted logistic regression model, provided there are enough responses for a meaningful analysis. The model will include the stratification factors WHO Performance Status (0/1) and Histology (squamous/non-squamous). The results of the analysis will be presented in terms of an odds ratio together with its associated 95% CI and 2-sided p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). CIs will be profile likelihood CIs (e.g. using the option 'LRCI' in SAS procedure GENMOD).

If there are not enough responses for a meaningful analysis using logistic regression then a Fisher's exact test using mid p-values will be presented.

For each treatment arm, best objective response (BoR) will be summarised by n (%) for each category (CR, PR, SD, PD, NE). No formal statistical analyses are planned.

12.2.6 Duration of Response (DoR)

The median duration of response based on the investigator's assessment of RECIST will be summarised with corresponding 95% CIs split by treatment arm. Only patients who had a response will be included in these summary tables. Formal statistical testing between treatment groups will not be performed.

12.2.7 Patient reported outcomes (PRO)

12.2.7.1 Lung Cancer Symptom Scale (LCSS)

Time to symptom progression (ASBI) will be analysed as described for the primary analysis of PFS. However subgroup analyses, treatment interaction testing and sensitivity analyses will not be performed (with the exception of attrition bias).

Two additional sensitivity analyses will be performed for time to symptom progression (ASBI):

1) where RECIST progression is considered a symptom progression event

2) where patients are censored at RECIST progression provided symptom progression has not yet occurred

These analyses will be performed using a stratified log-rank test.

A summary of symptom improvement rate (ASBI) will be produced. Symptom improvement rate will be analysed as described for the analysis of ORR.

Supportive analyses will be performed for the individual symptoms from the ASBI. The symptom improvement rate for each of the 6 individual symptoms will be compared between treatment groups using a logistic regression model as described for ORR. The odds ratio and 95% CI for each symptom will be presented graphically on a forest plot. In addition, time to symptom progression for each of the 6 individual symptoms will be compared between treatment groups using a log-rank test as described for the primary analysis of PFS. The HR and 95% CI for each symptom will be presented graphically on a forest plot. P-values will not be calculated for these supportive analyses.

The individual item scores from the LCSS for symptom distress and interference with activity levels will be summarized using descriptive statistics only (formal statistical testing between treatment groups will not be performed). For each of the items, absolute values and change from baseline will be summarized over time for each treatment group. In addition, response rates for each treatment group will be summarized for each item.

12.2.7.2 Short-Form Health Survey (SF-36v2)

The scores for each of the 8 health domain scales and for each of the physical and mental component summary measures will be summarized in terms of mean changes from baseline at each post-baseline assessment with no formal statistical testing. The responses to each of the

health domain scales and summary measures will also be categorized in terms of improved, worsened, and stable at each post-baseline assessment. If less than 50% of the items in one domain are missing, the mean scores for the completed items will be used for imputation. If 50% or more of the items in one domain are missing, that subscale will be treated as missing.

An exploratory analysis of utility values derived using SF-36v2 scores may be undertaken. This would include descriptive statistics, graphs and listings reported for health state utility values by visits as well as change in these scores from baseline. To support future economic evaluations of selumetinib, additional appropriate analyses may be undertaken, for example, mean health state utility pre and post treatment and pre and post progression.

12.2.7.3 Healthcare Resource Use

An exploratory health economic analysis of hospital episodes including type of contact (hospitalisation, outpatient, day case), reason, length of stay (including ICU), concomitant medication and procedures and tests may be undertaken to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of selumetinib. This would include providing descriptive statistics as appropriate, including means, median and ranges.

12.2.8 Safety data

Safety and tolerability data will be presented by treatment received using the safety population.

Data from all cycles of initially randomised treatment will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient and treatment group. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial treatment group. The number of patients experiencing each AE will be summarised by treatment group and CTCAE grade.

- Other safety data will be assessed in terms of physical examination, clinical chemistry, haematology, vital signs, ophthalmological examination (best corrected visual acuity, intra-ocular pressure, slit-lamp fundoscopy), echocardiogram/MUGA and ECGs. Exposure to selumetinib and docetaxel will be summarized. Time on study and selumetinib and docetaxel dose interruptions and reductions will also be summarised. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

12.2.9 PK data

Selumetinib and N-desmethyl selumetinib concentration data will be listed for each patient and each dosing day but will not be summarised.

12.2.10 PK/PD relationships

If the data are suitable, the relationship between the plasma selumetinib and/or N-desmethyl selumetinib concentrations/exposure and efficacy/safety parameters may be investigated graphically or using appropriate PK/PD software.

12.3 Determination of sample size

PFS is the primary endpoint. However, the sample size is calculated based on characterise the overall survival benefit of selumetinib in combination with docetaxel.

Approximately 500 *KRAS* mutation positive patients will be randomised (1:1) to obtain approximately 325 death events (65% maturity). If the true OS HR for the comparison of selumetinib+docetaxel versus placebo+docetaxel is 0.72 (likely to correspond to a 38% prolongation of OS), the study has at least 80% power to demonstrate a statistically significant difference for OS, assuming a 2% 1-sided significance level (see Section 12.2.1 for details of the multiple testing strategy and control of the Type I error).

An OS HR of 0.72 corresponds to an approximate 2-month improvement in median OS over an estimate of 5.2 months for placebo in combination with docetaxel, assuming proportional hazards and exponential data distribution. A 2-month improvement in median OS is regarded as clinically meaningful. The smallest treatment difference that would be statistically significant at the 1-sided 2% level is an OS HR of approximately 0.80 (0.796 if exactly 325 OS events).

With this number of patients and if the true PFS HR is 0.58, the study will provide over 90% power to demonstrate a statistically significant difference for PFS with a 1-sided significance level of 2.5% (2-sided 5%) (corresponding to the estimated treatment effect observed in the Phase II study D1532C00016, based on 71 events and a difference in medians of 3 months).

12.4 Independent data monitoring committee

This study will use an external IDMC to perform ongoing safety analyses:

- The IDMC reviewed the safety data from approximately the first 50 patients of each treatment group when they had been followed for a minimum of 12 weeks (with the exception of patients who died or withdrew consent before completing 12 weeks in the study). This occurred approximately 14 months post first subject in (FSI).
- The IDMC conducted a second safety review 4 months after the first safety review. Both IDMC safety analyses resulted in a recommendation to continue as planned.
- The IDMC will review the safety data prior to the planned primary analysis.
- Additional reviews of the safety data may be requested by the IDMC at additional points during the study

This committee will be composed of therapeutic area experts and biostatisticians, who are not employed by AZ, and do not have any major conflict of interest.

Following the reviews, the IDMC will recommend whether the study should continue unchanged, be terminated, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AZ. The report will include the recommendation and any potential protocol amendments and will not contain any unblinding information.

A separate IDMC charter will be developed which will contain details of the IDMC members and clearly define the responsibilities of the IDMC.

The safety of all AstraZeneca clinical studies is closely monitored on an-ongoing basis by AstraZeneca representatives in consultation with the Patient Safety Department. Issues identified will be addressed; this could involve, for instance, amendments to the study protocol and letters to Investigators.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an 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 Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site.

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

13.2 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 is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

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

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

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 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 all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

13.3.2 Paternal exposure

The outcomes of any conception occurring from the date of the first dose, until 30 days after last dose, must be followed up and documented in the “Pregnancy Outcome Report” form.

Male patients must refrain from fathering a child during the study and 12 weeks following the last dose of selumetinib/placebo and in accordance with the docetaxel local prescribing information following last dose of docetaxel (see Section 5.1), since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated.

Pregnancy of the patients' partner is not considered to be an AE. However, the outcome of all pregnancies (including spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

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Clinical Study Protocol Appendix B

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Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

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 subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

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

- 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.

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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.

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Appendix D
Pharmacogenetics Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system
PGx	Pharmacogenetics

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the selumetinib clinical development programme to explore how genetic variations may affect the clinical parameters associated with selumetinib and/or agents used in combination or as comparators. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

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

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to selumetinib and/or agents used in combination and/or as comparators.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

All randomised patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study. An additional patient informed consent is required to collect a pharmacogenetics blood sample.

3.1.2 Inclusion criteria

See main Clinical Study Protocol Section 4.1.1.

3.1.3 Exclusion criteria

See main Clinical Study Protocol Section 4.2.1.

3.1.4 Discontinuation of patients from this genetic research

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

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main

study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at Visit 2 or after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1 of the Clinical Study Protocol.

3.3 Coding and storage of DNA samples

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

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

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 Informed consent

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

4.2 Patient data protection

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

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

5. DATA MANAGEMENT

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

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

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

7. LIST OF REFERENCES

None

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Appendix E
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 30 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 in Section 4.2of 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

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Appendix F
Patient Reported Outcome Questionnaires

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1. EXAMPLE LUNG CANCER SPECIFIC SYMPTOM QUESTIONNAIRE (LCSS)

LUNG CANCER SYMPTOM SCALE (LCSS): PATIENT SCALE

Directions: Please place a mark along each line where it would best describe the symptoms of your lung cancer DURING THE PAST DAY.

1. How is your appetite?
   As good as it could be — As bad as it could be
2. How much fatigue do you have?
   None — As much as it could be
3. How much coughing do you have?
   None — As much as it could be
4. How much shortness of breath do you have?
   None — As much as it could be
5. How much blood do you see in your sputum?
   None — As much as it could be
6. How much pain do you have?
   None — As much as it could be
7. How bad are your symptoms from lung cancer?
   I have none — As bad as they could be
8. How much has your illness affected your ability to carry out normal activities?
   Not at all — So much that I can do nothing for myself
9. How would you rate the quality of your life today?
   Very high — Very low

Note: Proper administration requires that each question be presented on a separate card. Contact Patricia J. Hollen for permission to use the copyrighted LCSS and for copying techniques (photocopying will distort the lines).
Reprinted from *European Journal of Cancer*, 29A(suppl 1), Hollen PJ, Gralla RJ, Kris MG, Potanovich LM, Quality of life assessment in individuals with lung cancer: testing the Lung Cancer Symptom Scale (LCSS), 551-558, 1993, with kind permission from Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington OX5 1GB, UK.

2. EXAMPLE SF-36V2- SHORT FORM HEALTH SURVEY – 36 ITEMS (VERSION 2)

AstraZeneca

Study Code: D1532C00079 **SF-36v2®** E-Code: E __ __ __ __/__ __ __

Date questionnaire completed: __ __ __ __/__ __ __/__ __ (YYYY / MMM / DD) Visit No. _____

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

 1/6

AstraZeneca

Study Code: D1532C00079 **SF-36v2®** E-Code: E __ __ __ __/__ __ __

Date questionnaire completed: __ __ __ __/__ __/__ __ (YYYY / MMM / DD) Visit No. _____

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

(SF-36v2® Health Survey Acute, United States (English)) 2/6

AstraZeneca

Study Code: D1532C00079 **SF-36v2®** E-Code: E __ __ __ __/__ __ __

Date questionnaire completed: __ __ __ __/__ __ __/__ __ (YYYY / MMM / DD) Visit No. _____

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

 3/6

AstraZeneca

Study Code: D1532C00079 **SF-36v2®** E-Code: E __ __ __ __/__ __ __

Date questionnaire completed: __ __ __ __/__ __ __/__ __ (YYYY / MMM / DD) Visit No. _____

6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past week?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

AstraZeneca

Study Code: D1532C00079 **SF-36v2®** E-Code: E __ __ __ __/__ __ __

Date questionnaire completed: __ __ __ __/__ __ __/__ __ (YYYY / MMM / DD) Visit No. _____

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Study Code: D1532C00079 **SF-36v2®** E-Code: E __ __ __ __/__ __ __

Date questionnaire completed: __ __ __ __/__ __ __/__ __ (YYYY / MMM / DD) Visit No. _____

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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Clinical Study Protocol Appendix G	
Drug Substance	Selumetinib (AZD6244; ARRY-142886)
Study Code	D1532C00079
Edition Number	2
Date	

Appendix G
Further Clarification on Previous Anti-Cancer Treatments in D1532C00079 Patient Population

1. FURTHER CLARIFICATION ON PREVIOUS ANTI-CANCER TREATMENTS IN D1532C00079 PATIENT POPULATION

Patients must have failed 1st line anti-cancer therapy or subsequently had a relapse of disease following 1st line therapy. The following is intended to provide guidance on what is considered failure of the 1st line anti-cancer therapy and definition of the 1st line treatment in the study so that patients will have met these eligibility criteria. If the investigator is in doubt about patient eligibility they should contact AstraZeneca for advice.

Target patient population:

Patients should have failed a 1st line anti-cancer treatment due to:

(a) Radiological confirmation of disease progression during treatment

Or

(b) Recurrent disease following completion of 1st line treatment

Patients should not have received 2nd line anti-cancer treatment and must be suitable to receive docetaxel for the 2nd line treatment in line with standard clinical practice.

Acceptable prior treatments:

- Patients will usually have received a platinum-based doublet. However those who have received a different 1st line anti-cancer combination regimen or 1st line single agent anti-cancer treatment will be accepted.
- Patients who had disease progression while on continued* maintenance therapy (maintenance using an agent in the first-line regimen) are eligible. Patients who had disease progression while on switch* maintenance therapy (maintenance using a different agent not used in the first-line regimen) are not eligible.

  ***According to NCCN guidance (Version 1 2014): Continuation maintenance refers to the use of at least one of the agents given in the first line, beyond 4-6 cycles, in the absence of disease progression. Switch maintenance refers to the initiation of a different agent, not included as part of the first line regimen, in the absence of disease progression, after 4-6 cycles of initial therapy.**

- Patients who had disease progression while on continuation maintenance therapy are eligible, but patients who had disease progression while on switch maintenance therapy are not eligible
- Radiotherapy alone is not counted as a line of therapy.

- Radiosensitisers and/or intrapleural administration of anti-cancer agents are not counted as a line of therapy.

- Patients who previously received chemoradiotherapy and had a recurrence and evidence of stage IIIB-IV disease **within 1 year*** of completing chemoradiotherapy will be eligible. Those patients who have received 2-3 cycles of further consolidation chemotherapy with the same or different agents will also be eligible if they progressed **within 1 year*** of completion of consolidation treatment.

- Patients who received adjuvant/ neoadjuvant chemotherapy and had a recurrence and evidence of stage IIIB-IV disease **within 6 months**** of completing chemotherapy will be eligible.

** Those patients who progress greater than 1 year after completing chemoradiotherapy, or greater than 6 months after completing adjuvant or neoadjuvant treatment may be suitable for re-challenge with platinum-based therapy as a 1st line treatment for advanced disease. However, if in the opinion of the investigator such patient is eligible to receive the 2nd line treatment, their participation in the study can be discussed on a case-by-case basis with the AstraZeneca Study Team Physician.

Appendix H
Cockcroft-Gault Formula

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 4.1, Inclusion 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.

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Clinical Study Protocol Appendix I	
Drug Substance	Selumetinib (AZD6244; ARRY-142886)
Study Code	D1532C00079
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Appendix I
Guidance for Management of Specific Adverse Events in Studies of Selumetinib (AZD6244; ARRY-142886)

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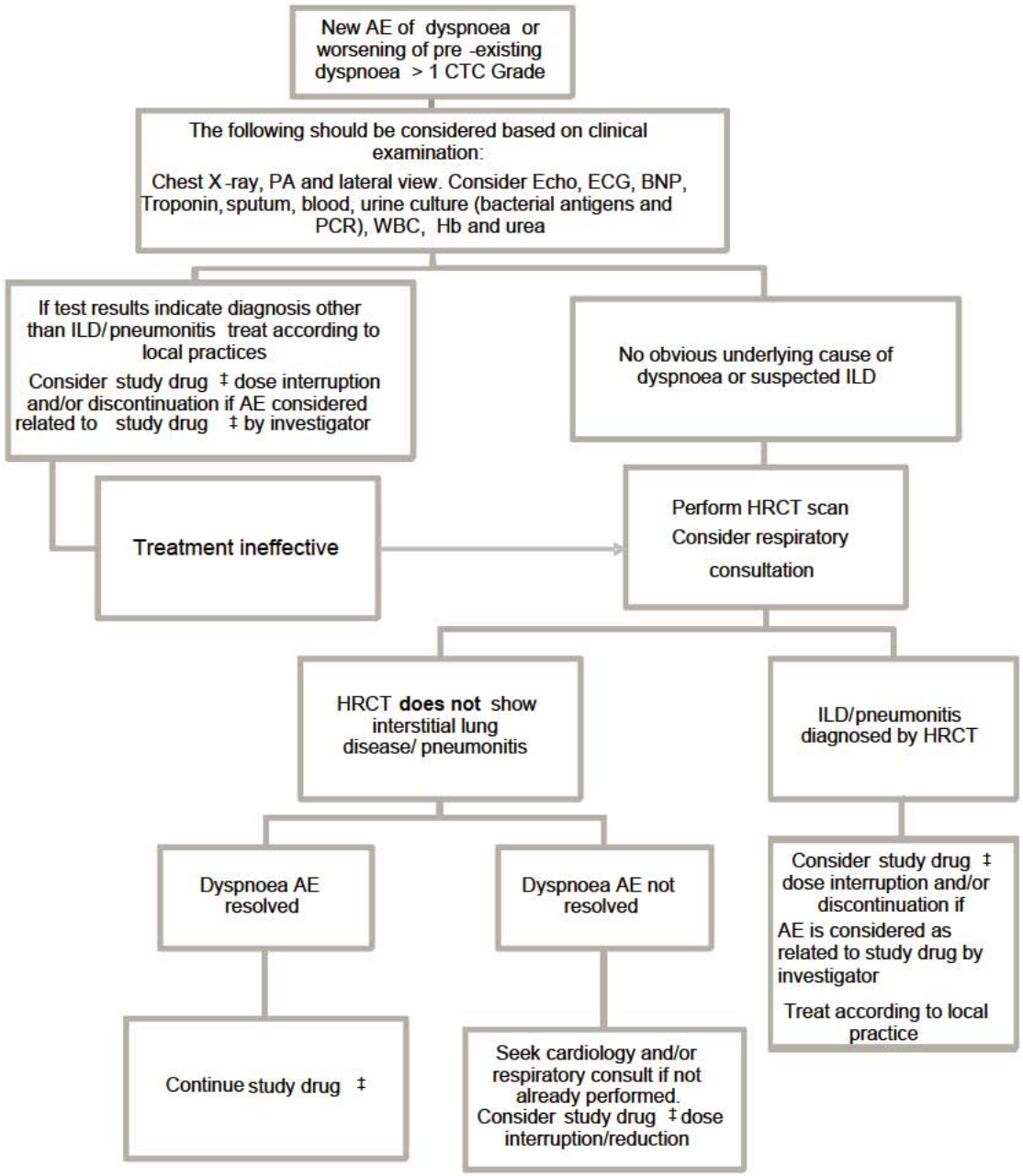

BNP: Brain Natriuretic Peptide
CTC: National Cancer Institute common toxicology criteria
Echo: Echocardiography
Hb: Haemoglobin
HRCT: High resolution computerised tomography
ILD: Interstitial Lung Disease
PA: posteroanterior
PCR: Polymerase chain reaction
WBC: White blood cells

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2. RECOMMENDATIONS FOR DIARRHOEA MANAGEMENT

Diarrhoea may occur during treatment with selumetinib and action should be taken as soon as symptoms develop. The recommendations for diarrhoea management are based on guidelines from the American Society of Clinical Oncology (J Clin Oncol 2004; 22:2918-26). These guidelines recommend that treatment-induced diarrhoea should be carefully monitored and treated aggressively to ensure that severe complications are avoided and that treatment is not delayed.

- Patients should be made aware that they are likely to experience diarrhoea and be encouraged to record the number of stools and report possible associated symptoms
- Patients should be given loperamide (in accordance with local regulation and local practice) to take home with them and be advised to start immediately after the first episode of unformed stool.
- Patients should be given dietary advice in case of diarrhoea (e.g. BRAT [bananas, rice, apple sauce, toast, plain pasta] diet; readily digestible food; avoidance of lactose-containing products, fried, fatty or spicy food) and increase fluid intake (8–10 glasses of clear fluids daily, including water and fluids containing salt and sugar, such as sports drinks and clear broth).
- Patients should seek advice early, from their physician or study nurse, if
  - Persistent Grade 1 or 2 diarrhoea (see Section 2.2) or
  - Grade 3 or 4 diarrhoea
  - Diarrhoea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension.

Table 1 CTCAE (version 4) grading for diarrhoea

CTCAE Grade	Patients without colostomies	Patients with colostomies
Grade 1	Increase in number of loose stools per day (<4)	Mild increase in loose watery colostomy output compared with pre-treatment
Grade 2	Increase in number of loose stools per day (4-6) or nocturnal episodes	Moderate increase in loose watery colostomy output compared with pre-treatment, not interfering with normal activity
Grade 3	Increase of more than 7 loose stools per day or incontinence or needing support for dehydration	Severe increase in loose watery colostomy output compared with pre-treatment and interfering with normal activity
Grade 4	Life-threatening consequences (e.g. hemodynamic collapse)	

2.1 Initial management of uncomplicated Grade 1 or 2 diarrhoea

- Patients should **immediately** start loperamide after the first episode of diarrhoea (4 mg initially) and continue loperamide (2 mg every 4 hours or after each unformed stool) until they have been free from diarrhoea for at least 12 hrs

- If **after 12 hours of loperamide treatment** the diarrhoea is not improving or resolved, the patient should be instructed to contact the centre and to increase to high dose loperamide (2 mg every 2 hours, or 4 mg every 4 hours at night) and continue to take loperamide until they have been free from diarrhoea for at least 12 hrs. Additional treatment may be considered according to local practice.

Note: should not exceed 16mg loperamide (i.e. 8 capsule/tablets) over a 24-hour period.

2.2 Management of persistent (>24h) Grade 1 or 2 diarrhoea despite loperamide at high dose

The patient should be seen by the physician or study nurse for full evaluation and the following should be considered:

- Rehydration and electrolytes replacement as appropriate

- Infectious causes and aetiologies such as Clostridium difficile or viral gastroenteritis;

- Antibiotics if appropriate (for example an oral fluroquinolone for 7 days) particularly if the patient is neutropenic ($<1 \times 10^9$/L) or has a fever;

- Discontinuation of loperamide and start of octreotide (Sandostatin);

It may also be appropriate to consider:

- Addition of other second-line anti-diarrhoeal agents according to local practice

- Selumetinib or matching placebo interruption until resolution of the diarrhoea

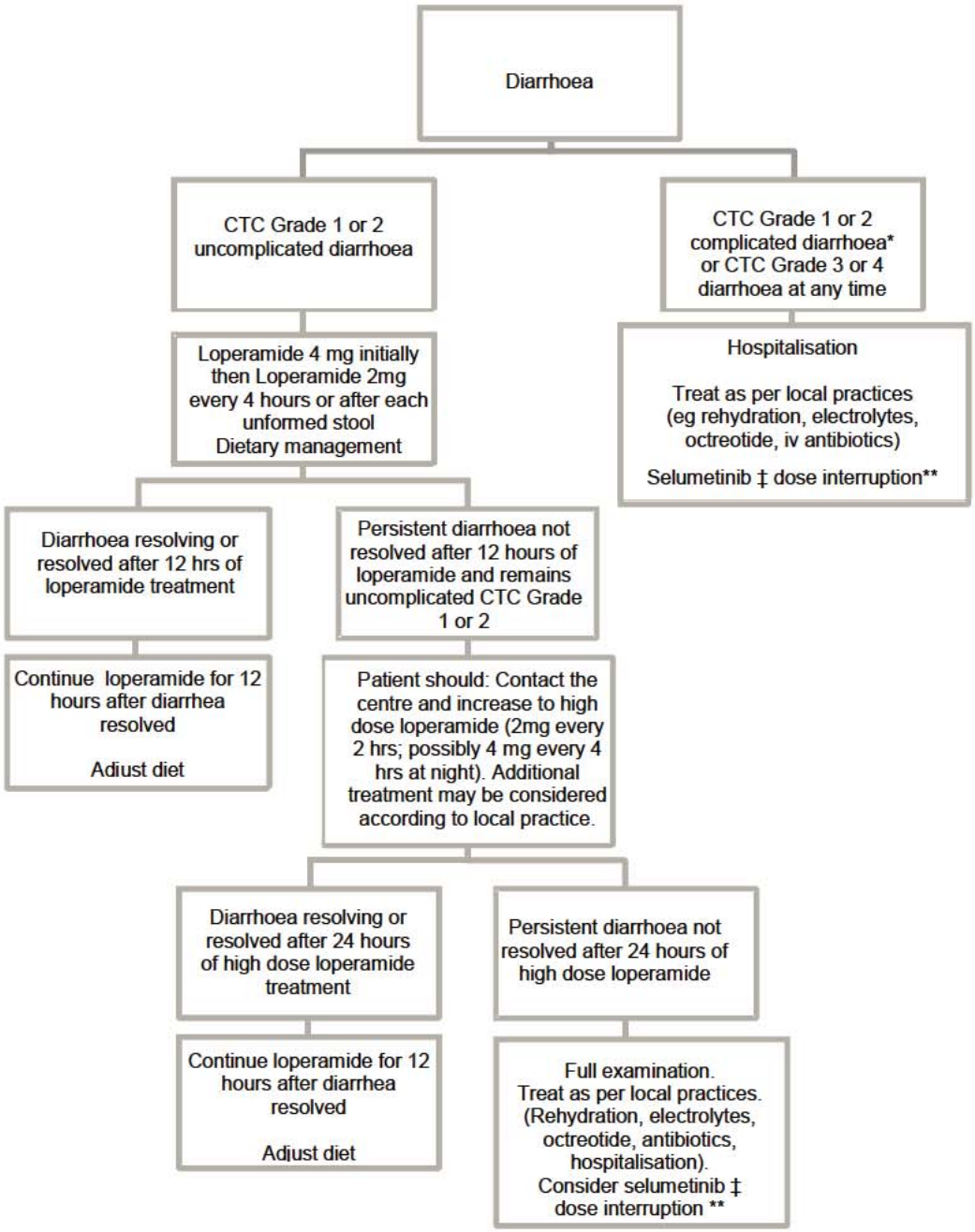
- Hospitalisation

In studies involving combination of selumetinib (or matching placebo) with other anti-cancer treatment, interruption or delay of the combination agent may be considered according to manufacturer's guidance or local practice

2.3 Management of any grade uncontrolled or complicated diarrhoea, or Grade 3-4 diarrhoea

- Hospitalisation and full evaluation
- Intravenous fluids, electrolytes and antibiotics if needed (e.g. fluroquinolone)
- Interrupt selumetinib (or matching placebo) until diarrhoea and associated symptoms resolve
- Start octreotide (Sandostatin)
- Interruption or delay of docetaxel according to manufacturer's guidance or local practice.

Figure 1 Guidance for the management of patients with diarrhoea



*Diarrhoea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension
****Consider interruption or delay of combination anticancer agent if applicable**
‡ selumetinib or matching placebo

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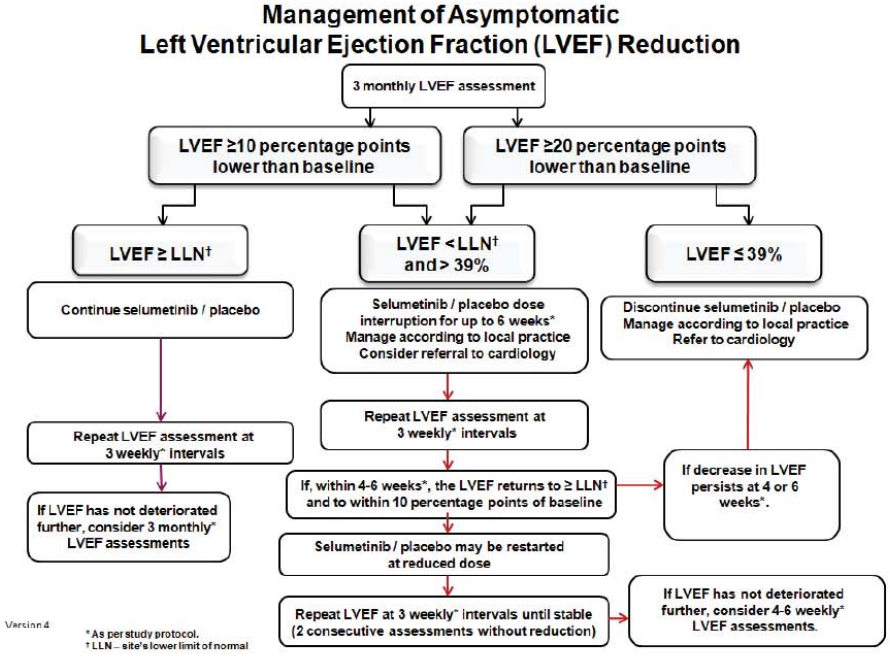
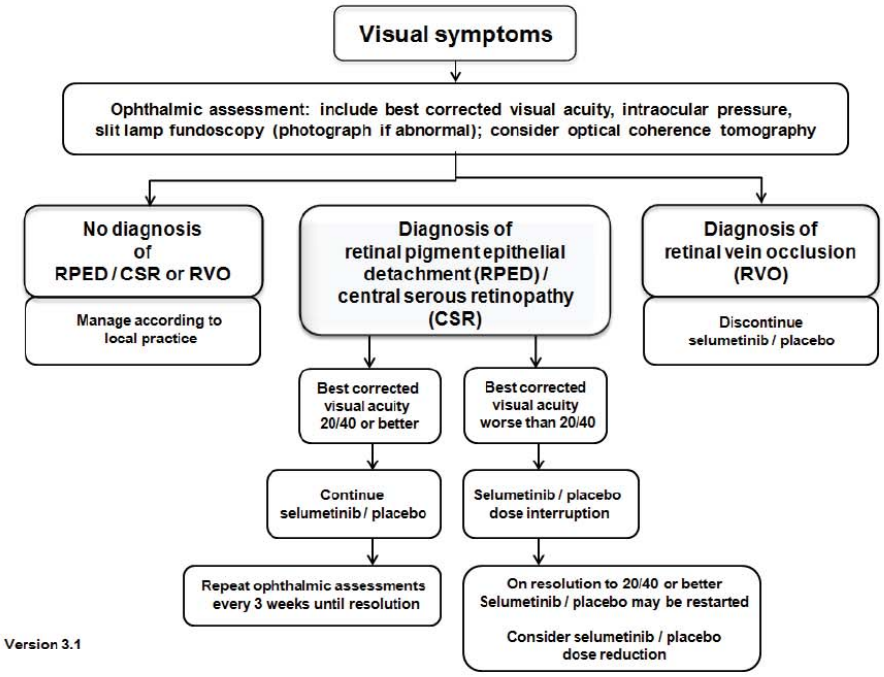
3. GUIDANCE FOR MANAGEMENT OF PATIENTS WITH A REDUCTION IN LVEF



4. GUIDANCE FOR MANAGEMENT OF PATIENTS WITH VISUAL SYMPTOMS OR ABNORMAL FINDINGS



5. GUIDANCE FOR THE MANAGEMENT OF PATIENTS WITH RASH

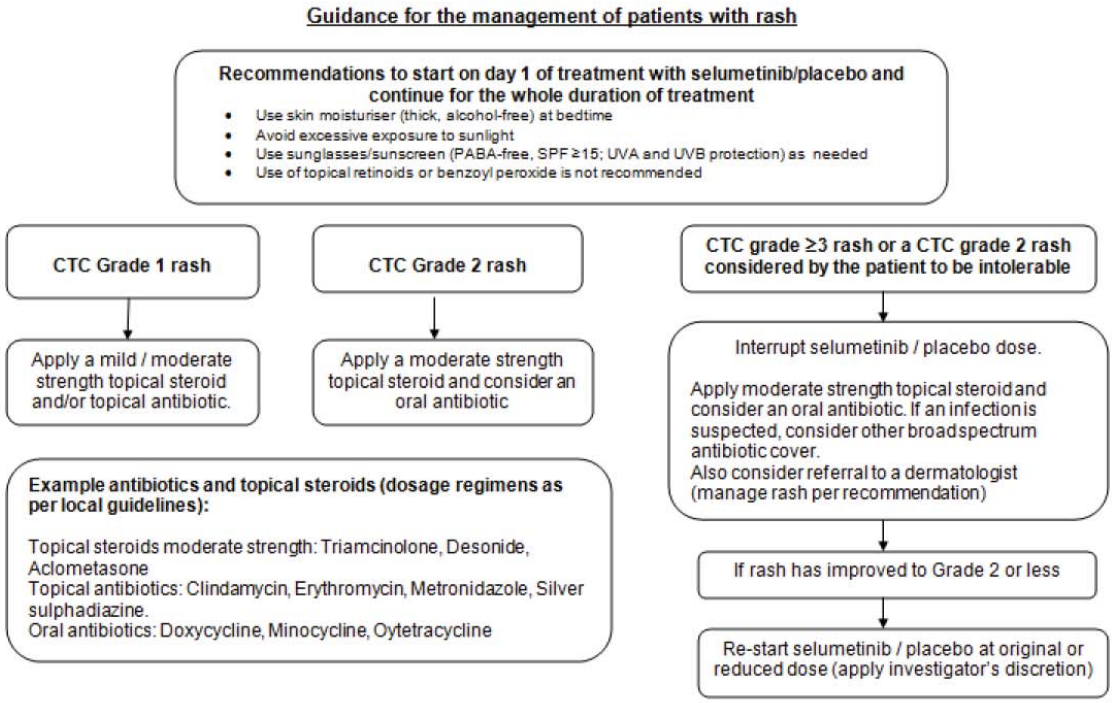


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Table 2 Example topical steroids and antibiotics (use according to local guidelines)

Topical steroids moderate strength	Triamcinolone acetonide 0.025% Fluticasone proprionate 0.05%	Desonide 0.05% Aclometasone 0.05%
Topical antibiotics	Clindamycin 1 - 2% Metronidazole 1%	Erythromycin 1% - 2% Silver sulphadiazine 1%
Oral antibiotics	Doxycycline 100 mg bd Oxytetracycline 500 mg bd	Minocycline 100 mg bd

‡ selumetinib or matching placebo
Version: Final 2.0

6. ORAL CARE RECOMMENDATIONS FOR PATIENTS TREATED WITH SELUMETINIB

Patients should be encouraged to take responsibility for their own oral care wherever possible. This may require frequent encouragement and education. The general recommendations of Rubenstein EB et al (2004)) are to maintain a clean and pain-free mouth, which reduces patient discomfort and helps prevent infection and promote dietary intake. Evidence from the literature regarding implementation and efficacy of oral protocols and patient education, suggest that patients who are taught oral care protocols perform oral care more diligently, take more responsibility for their care and may show an improvement in oral symptoms.

Prevention, early diagnosis and management of stomatitis may reduce the need for dose interruption and / or reductions of the study medications due to severe stomatitis and so allow the patient to continue on the study drugs. It is strongly recommended that patients receive advice regarding daily oral health care regimes, both before and during treatment.

6.1 Mouthwashes

Patients with a healthy mouth may use non-alcoholic mouthwash several times (4 to 6 times daily, or according to the instructions) daily e.g. after each meal during the study.

Saline mouthwashes (Sodium chloride 0.9%) should be preferred in cases of stomatitis, and should be used at a different time to toothbrushing e.g. after tea.

Use of a mouthwash immediately after selumetinib intake is recommended.

The tongue can be gently brushed (if not sore) with a soft toothbrush.

Patients with, or at risk of stomatitis should not use commercial / over-the-counter mouthwashes because of the alcohol content and astringency. Chlorhexidine mouthwashes are not recommended for the treatment of established stomatitis.

The mouth should be regularly inspected by the patient and healthcare professionals.

6.2 Smoking

Smoking should be strongly discouraged; patients should be offered help with smoking cessation if necessary in the form of nicotine replacement therapy or referral to smoking cessation services.

6.3 Alcohol intake

A **high alcohol** intake should be discouraged and patients advised to avoid painful stimuli such as spicy foods, hot food and drink.

6.4 Dental care

Dentate patients:

- Patients who are free from dental problems may be at less risk of stomatitis.
- Teeth should be brushed twice daily with a fluoride toothpaste and soft toothbrush, in the morning before breakfast and last thing in the evening before bed, about 30 minutes after eating. Toothbrush should be replaced regularly at least every 3 months but patients with stomatitis should change their toothbrush every 4 - 6 weeks.
- Use of soft toothbrush is recommended.
- Dental floss should be used once daily (caution in patients with coagulopathies including a low platelet count).

Edentulous patients:

- Dentures should be left out whilst at rest.
- Dentures should be cleaned thoroughly twice daily (before and after soaking overnight) and after every meal using a soft toothbrush and denture cleaner water.
- Dentures should be soaked overnight in a mild denture-soaking solution.

6.5 Sore mouth or stomatitis

In the event of sore mouth or stomatitis:

- Consider treating stomatitis at an early stage (CTCAE grade 1) or as soon as the patient complains of a sore mouth.

- Consider using oral topical analgesic anaesthesia with or without topical steroids, antiviral and/or antifungal medications depending on the patient's clinical condition and the local standard medical practice.

7. MANAGEMENT OF EVENTS OF SERUM CREATINE KINASE INCREASED (RAISED CREATINE PHOSPHOKINASE) AND POSSIBLE MUSCLE SYMPTOMS

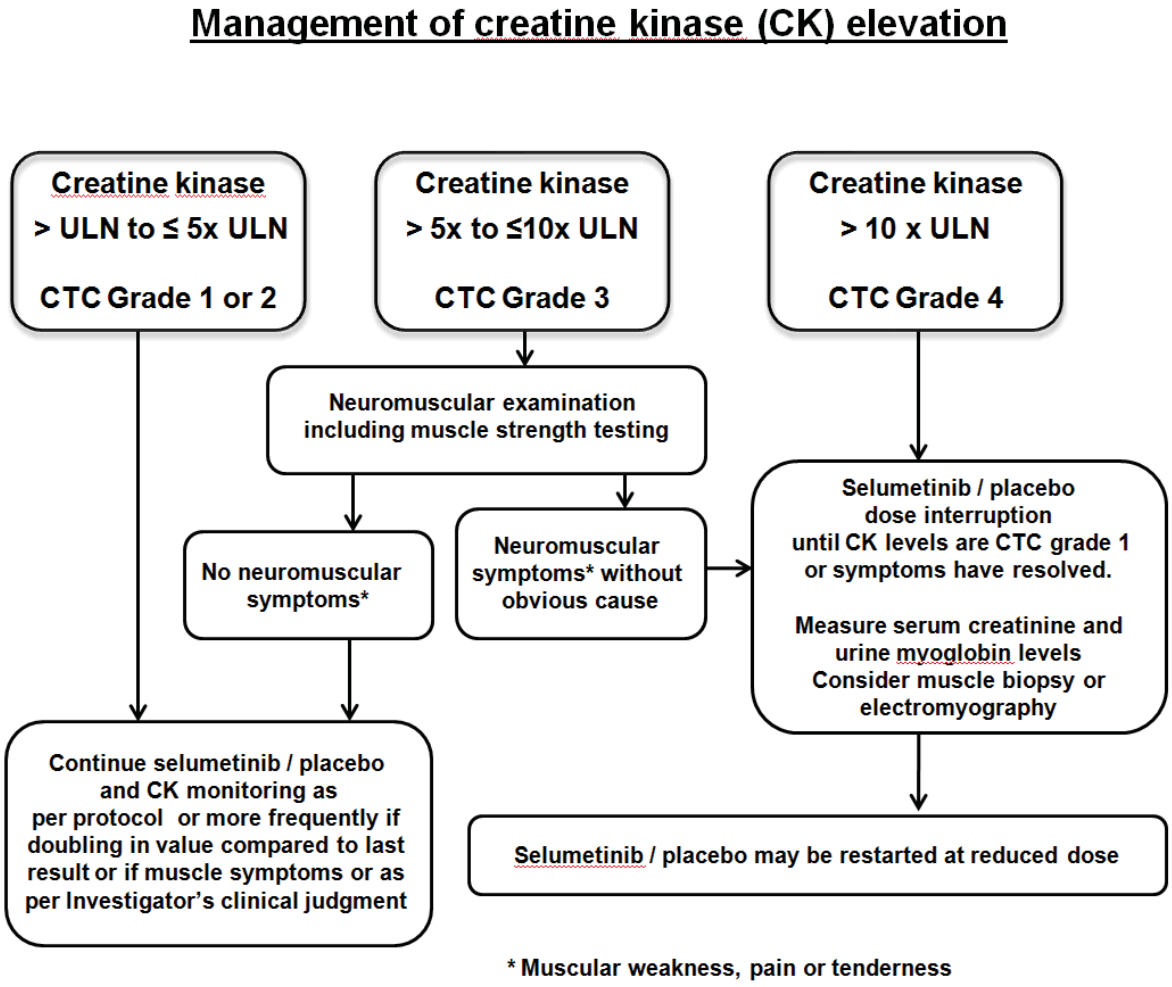
Abnormal laboratory values of serum creatine kinase (CK) / CPK elevation have been reported in patients receiving treatment with some MEK inhibitors. The CK enzyme is released from a number of tissue types, including skin and muscle. However, for patients receiving treatment with MEK inhibitors, the exact source of this enzyme is unknown. In order to minimise possible consequences associated with CK elevation that may potentially be arising from a muscular source, AZ recommends the management guidelines as described below. Additionally, laboratory values of 'CK increased' should only be reported as AEs if they fulfil any of the criteria for a serious AE, or if they are the reason for discontinuation of treatment with selumetinib.

Muscular symptoms concurrent with CK elevation should be reported as AEs. If appropriate, the definitions described in Table below should be applied:

Table 3 Muscle symptoms with possible creatine kinase increased

Adverse event term	Description / definition:
Myopathy	CK >10 x ULN (CTC Grade 4) CK >5 x ULN (CTC Grade 3) with muscle symptoms
Rhabdomyolysis	CK >10 x ULN (CTC Grade 4) and all of the following: muscle symptoms, myoglobinuria or renal impairment (serum creatinine 2 x baseline, or above ULN)

Figure 2 Guidance for the management of creatine kinase (CK) elevation



8. LIST OF REFERENCES

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Peterson et al , Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines Annals of Oncology 2010; 21(Suppl 5): v261–v265

Rubenstein EB et al (2004)
Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 2004;100(9):2026–2046

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Clinical Study Protocol Appendix J

Drug Substance	Selumetinib (AZD6244; ARRY-142886)
Study Code	D1532C00079
Edition Number	1
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Appendix J
Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours)

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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 computed tomography (CT) or magnetic resonance imaging (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 of the chest and abdomen (including adrenal glands) will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For 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 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

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

3.7 Cytology and histology

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

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

3.8 Isotopic bone scan

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

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

3.9 FDG-PET scan

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

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

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. Follow-up assessments should be performed every 6

weeks (± 1 week) relative to date of randomisation until objective disease progression as defined by RECIST 1.1. (see Study Plan from Study Protocol).

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. This schedule is to be followed in order to minimise an unintenial bias caused by some patients being assessed at a different frequency than other patients.

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 5 mm.
- 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 5 mm.
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 be 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

N/A

6. REFERENCES

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Clinical Study Protocol Appendix K	
Drug Substance	Selumetinib (AZD6244; ARRY-142886)
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Edition Number	1
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Appendix K
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

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