Revised Clinical Study Protocol

Drug Substance	AZD6244
Study Code	D1532C00067
Edition Number	2
Date	

A Phase I, Open-Label Study to Investigate the Safety and Tolerability of AZD6244 (Selumetinib) When Given as a Monotherapy in Japanese Patients with Advanced Solid Malignancies, and When Given in Combination with Docetaxel as 2nd line therapy in Japanese Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB-IV)

Sponsor:

AstraZeneca

AstraZeneca Research and Development site representative

Study Leader

Date
(DD MM YYYY)

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

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

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

Principal Investigator(s)

Name and address of principal investigator are shown in Supplement A.

For contact details of AstraZeneca personnel see Section 20.1

INTRODUCTION & STUDY FLOW CHART

A Phase I, Open-Label Study to Investigate the Safety and Tolerability of AZD6244 (selumetinib) When Given as a Monotherapy in Japanese Patients with Advanced Solid Malignancies, and When Given in Combination with Docetaxel as 2nd line therapy in Japanese Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB-IV)

Introduction

AZD6244 is a potent, selective, uncompetitive inhibitor of MEK that acts on cancer cells driven by excess activity transmitted via RAF/MEK/ERK protein kinase signalling pathway.

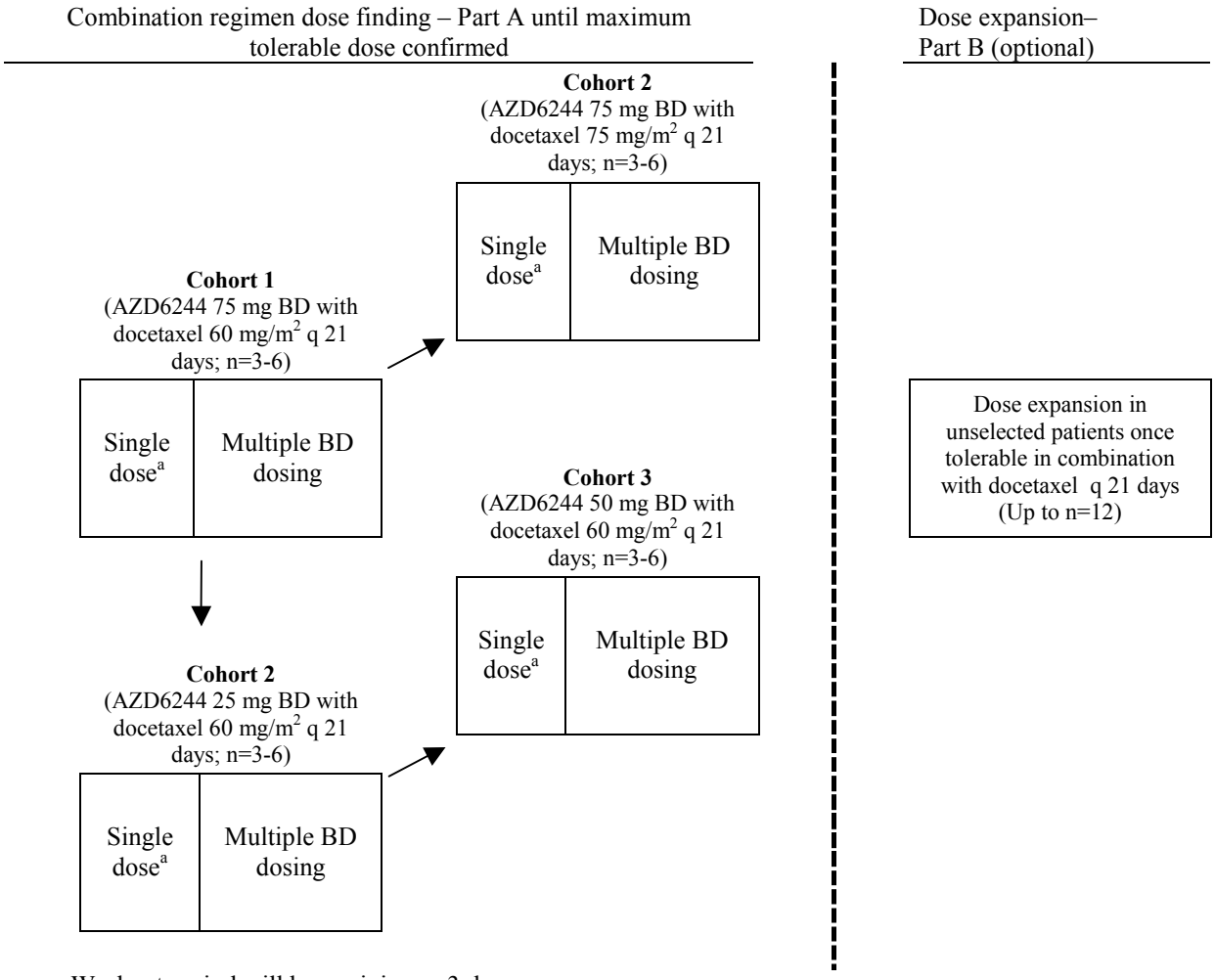
As of 31 January 2013, AZD6244 has been administered in approximately 1640 cancer patients in overseas clinical studies of AZD6244 given as a monotherapy and in combination therapies in non-Asian patients with advanced non-small cell lung cancer (NSCLC).

The objective of the combination therapy part of this study will be to investigate the safety and tolerability of AZD6244 given in combination with docetaxel as 2nd line therapy in Japanese patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB-IV). In addition, the pharmacokinetic profile of AZD6244 and docetaxel will be investigated.

Following the combination regimen dose escalation phase (Part A) of the study additional patients may be enrolled to a dose expansion phase (Part B) to refine further the safety, tolerability, pharmacokinetics and biological activity of the combination in this patient population.

The objective of the monotherapy part of this study will be to investigate the safety and tolerability of AZD6244 given as a monotherapy in Japanese patients with advanced solid malignancies. In addition, the pharmacokinetic profile of monotherapy AZD6244 will be investigated.

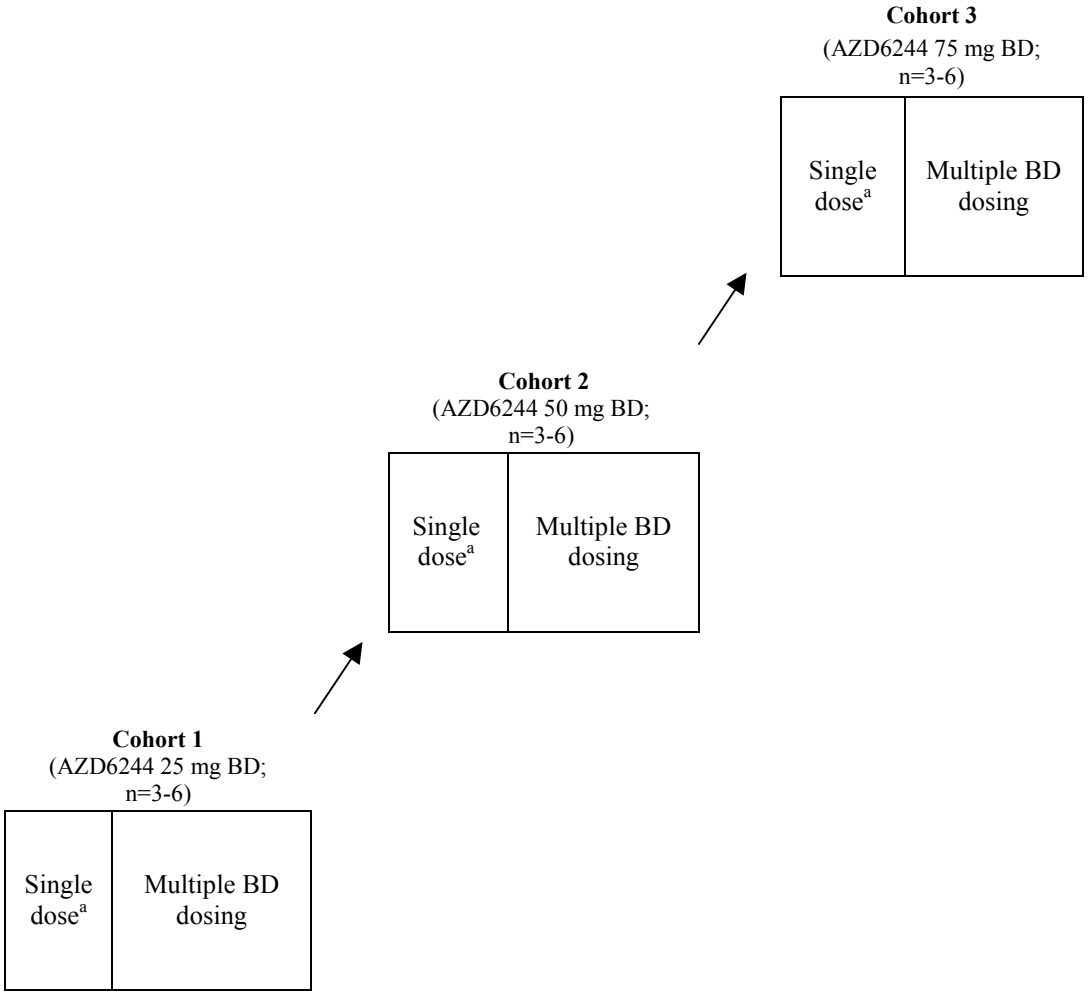
Flow chart : Combination therapy part (see Section 3.1)



a Washout period will be a minimum 3 days.

Flow chart : Monotherapy part (see Section 9.1)

Monotherapy dose finding–
until maximum tolerable dose confirmed



a Washout period will be a minimum 3 days.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 13.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AZKK	AstraZeneca KK Japan
BD (bd)	twice daily
BRAF	*v-raf* murine sarcoma viral oncogene homolog B1
CFDNA	Circulating free tumour deoxyribonucleic acid
CPD	Clinical Pharmacology, Drug Metabolism and Pharmacokinetics
CR	Complete response
CRF	Case Report Form (electronic/paper)
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology group
EGFR	Epidermal Growth Factor Receptor
ERK	Extracellular signal-regulated kinase
FSH	Follicle stimulating hormone
FTIP	First Time in Patients
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
GMP	Good Manufacturing Practice

Abbreviation or special term	Explanation
Hb	Hemoglobin
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
IB	Investigators Brochure
ICH	International Committee on Harmonisation
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LH	Luteinizing hormone
LKB1	Liver kinase B1
LVEF	Left ventricular ejection fraction
MAP	Mitogen-activated protein
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple Gated Acquisition scan
NE	Not evaluable
NSCLC	Non-small-cell lung cancer
NTL	Non-target lesion
ORR	Objective response rate
p53	protein 53
PD	Progression of disease
PGx	Pharmacogenetics
PK	Pharmacokinetics
PR	Partial response
QRS	QRS wave (QRS complex) by Electrocardiogram
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
Raf	v-raf murine sarcoma viral oncogene homolog
Ras	Ras protein
RECIST	Response Evaluation Criteria in Solid Tumours

Abbreviation or special term	Explanation
RNA	Ribonucleic Acid
R-R	Interval between R wave and the following R wave by Electrocardiogram
SAE	Serious adverse event (see definition in Section 13.2)
SD	Stable disease
SRC	Safety Review Committee
STD_{10}	Severely Toxic Dose in 10% of rodents
TL	Target lesion
ULN	Upper limit of normal
WBDC	Web Based Data Capture
WHO	World Health Organisation

Combination Therapy Part: Sections From 1 to 6

1. STUDY OBJECTIVES (COMBINATION THERAPY PART)

1.1 Primary objective

To investigate the safety and tolerability of oral doses of AZD6244 when administered in combination with docetaxel on day 1 of every 21 day cycle in Japanese patients with 2nd line NSCLC.

1.2 Secondary objective(s)

To evaluate the pharmacokinetics of AZD6244 and docetaxel when dosed together.

1.3 Exploratory objective(s)

To define the recommended combination dose for future studies of AZD6244 in combination with docetaxel on day 1 of every 21 day cycle in Japanese patients.

To analyse biological samples (eg, biopsy, archived tumor, serum/plasma) for factors, which may influence the response to AZD6244 (or docetaxel), such as genetic variability, gene expression profile, protein expression profile etc.

To collect a blood sample for DNA extraction and storage to provide data to investigate whether variability in the PK, safety, or efficacy results could be explained by differences in the patient's genotype or phenotype.

To make a preliminary assessment of tumor response as measured by Objective Response Rate (ORR) per investigators assessment using RECIST 1.1 when AZD6244 is given in combination with docetaxel in Japanese patients with 2nd line NSCLC.

2. BACKGROUND

2.1 Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the most common cancer in terms of incidence (12 million new cases or 12.3% of the world's annual total cancer cases) and mortality (1.1 million deaths annually) (Parkin 2001). NSCLC represents approximately 80% to 85% of all lung cancers (Gridelli et al 2005). Unfortunately, at the time of diagnosis approximately 70% of NSCLC patients already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of early stage NSCLC patients who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters & Le Chevalier 2005).

A number of molecular abnormalities have been shown to be characteristic of certain lung cancers. 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 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 EGFR tyrosine kinase inhibitors (Massarelli et al 2007, Miller at al 2008, Pao et al 2005) and erlotinib combined with chemotherapy (Eberhard et al 2005).

Despite advances in diagnosis, imaging, staging and treatment, estimated overall five-year survival for patients with NSCLC is 16%. In the advanced NSCLC population 5-year survival varies from 20% to 25% in stage IIIA disease to only 3% to 5% in stage IIIB disease (Allen et al 2008). Once patients experience treatment failure with initial therapy, response to further systemic treatment is approximately 10% (Hanna et al 2004).

To date, none of the commonly used chemotherapeutic regimens in treatment of advanced NSCLC demonstrated clear superiority over others (Schiller et al 2002). A better understanding of the role of cellular signalling pathways in lung carcinogenesis and development of targeted agents holds promise in treating patients with advanced NSCLC.

2.1.1 NSCLC treatment in Japan

Lung cancer is the leading cause of cancer-related deaths in Japan. Most of NSCLC patients are inoperable at diagnosis. Despite advances of surgery, chemotherapy, molecular target agents and radiotherapy, overall 5-year survival rate still remains at only 16.7% and 5.8% in NSCLC Stage IIIB-IV respectively (Sawabata et al 2010).

Docetaxel is the current standard second-line chemotherapy for advanced NSCLC. However its monotherapy efficacy is very limited and new combination regimen using docetaxel iv 75 mg/m^2 q 21 days has been investigated worldwide including Japan (Daga et al 2011).

2.2 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 signals from multiple pathways, resulting in an effect on tumour proliferation, differentiation and survival.

2.3 AZD6244 (selumetinib)

AZD6244 is a potent, selective, uncompetitive inhibitor of MEK, licensed for development by AstraZeneca Pharmaceuticals from was responsible for the first administration into man study, performed at three centres in the United States. The

remainder of the clinical development programme for oncology indications is the responsibility of AstraZeneca. Phase II monotherapy studies commenced in 2006.

2.4 Non-clinical information and correlative studies

2.4.1 Pre-clinical experience with AZD6244

Non-clinical experience with AZD6244 is described in the current version of the AZD6244 Investigator's Brochure; non-clinical experience with AZD6244 in lung cancer models and in combination with docetaxel is summarised below.

AZD6244 had strong anti-tumour activity in multiple non-clinical models, including human lung cancer tumours (Calu-6). AZD6244 has demonstrated potent inhibition of *BRAF* or *KRAS* positive cell line viability and inhibition of xenograft growth both as monotherapy and in combination with a number of cytotoxic and targeted agents, including docetaxel. In three xenograft models of a *KRAS* positive tumour (SW620 colorectal cancer, HCT-116 colorectal cancer and A549a NSCLC), a beneficial effect of the combination of AZD6244 with cytotoxic drugs (eg, docetaxel and temozolomide) or targeted agents (eg, gefitinib) was observed when compared with either agent as monotherapy.

2.4.2 Clinical experience

Clinical experience with AZD6244 as monotherapy and in combination with other anti-cancer agents is described in the current version of the AZD6244 Investigator's Brochure. Clinical experience with AZD6244 in combination with docetaxel is summarised below.

The combination of AZD6244 and docetaxel (75 mg/m^2 every 21 days) has been investigated in a Phase I study (D1532C00004) in 35 non-Asian patients with advanced solid tumours (Kim et al 2011, EORTC-AACR abstract). Combination therapy did not appear to affect the pharmacokinetics of AZD6244 or docetaxel. The tolerability profile of the combination treatment was largely consistent with AZD6244 or docetaxel administered as monotherapy: the most common AEs were peripheral oedema (71%), diarrhoea (69%), fatigue (63%), nausea (49%), vomiting (46%), neutropenia (43%), and dermatitis acneiform (40%). The most common grade ≥3 AEs were haematological events (51%), infections (26%), fatigue/asthenia (23%), peripheral oedema (10%), and gastrointestinal events (10%). Dose-limiting toxicities of neutropenia and febrile neutropenia were reported, and AZD6244 75 mg bd with docetaxel 75 mg/m^2 (without GCSF primary prophylaxis) was the recommended Phase II dose. Clinical responses were observed in 5/28 pts (18%) receiving AZD6244 75 mg bd with docetaxel.

AZD6244 75 mg BD with docetaxel (75 mg/m^2 every 21 days) 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 AZD6244+docetaxel compared with those receiving placebo+docetaxel, and statistically significant improvements in favour of AZD6244 were observed for the

secondary endpoints of progression-free survival, objective response rate and patients alive and progression free at 6 months (data on file).

The most common adverse events in patients receiving AZD6244+docetaxel in Study D1532C00016 were consistent with the monotherapy profiles of each agent: diarrhoea (72.7%), infections (50.0%), nausea (43.2%), vomiting (43.2%), peripheral oedema (40.9%), rash (mainly dermatitis acneiform, 38.6%) and stomatitis (oral mucositis, 36.4%). Neutrophil counts below the lower limit of normal were reported in similar proportions of patients in each treatment group (86.1% vs 78.6%). Higher incidences of CTCAE grade 4 low neutrophil counts (44.2% vs 23.8%), febrile neutropenia (15.9% vs 0%) and CTCAE grade 3 infections (20.5% vs 2.4%) were reported in patients receiving AZD6244+docetaxel compared with those receiving placebo+docetaxel. The incidence of deaths due to adverse events was low and similar between treatment groups (9.1% vs 7.1%); CTCAE grade 5 events were respiratory failure and pneumonia in the AZD6244+docetaxel group (none considered related to AZD6244 by the Investigator), and respiratory failure+pneumonitis and cardiac arrest in the placebo+docetaxel group (data on file).

This section lists those events that are to be regarded as expected for regulatory reporting purposes as documented in Section 5.4 of the Investigator Brochure.

- Gastrointestinal: diarrhoea, nausea, vomiting, stomatitis (oral mucositis), dry mouth.
- Skin and subcutaneous: rashes (including dermatitis acneiform and exfoliative rash), dry skin, paronychia.
- General: facial and/or peripheral oedema, fatigue/asthenia, pyrexia.
- Respiratory: dyspnoea.
- Eye: blurred vision.
- Physical assessments: increased blood pressure, reduced left ventricular ejection fraction.
- Laboratory changes: increases in serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT), hypoalbuminemia, hyperphosphataemia, which may be associated with an increase in calcium x phosphate product requiring therapeutic intervention.

In combination with docetaxel:

- Haematological: a higher incidence of febrile neutropenia has been reported in patients receiving AZD6244 in combination with docetaxel than in patients receiving placebo plus docetaxel.

- Haematological: a higher incidence of CTCAE Grade 4 low neutrophil counts has been reported in patients receiving AZD6244 in combination with docetaxel than in patients receiving placebo plus docetaxel.

3. STUDY DESIGN AND RATIONALE

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

3.1 Overall study design and flow chart

This is a Phase I, open-label study to investigate the safety, tolerability and pharmacokinetic profile of oral doses of AZD6244 when administered in combination with docetaxel (iv on day 1 of every 21 day cycle) as 2nd line therapy in Japanese patients with advanced NSCLC.

Adult Japanese patients with histologically or cytologically confirmed NSCLC that has progressed despite standard 1st line therapy AND who are eligible for docetaxel therapy will be enrolled onto the study.

Approximately 24 Japanese patients with 2nd line NSCLC will be recruited from 2-3 sites in Japan.

The study consists of two parts: a combination regimen dose escalation part (Part A) and a dose expansion part (Part B; optional). If the combination regimen of AZD6244 and docetaxel is determined to be tolerated in part A, then the dose expansion (Part B) may commence using the highest tolerated dose from the escalation (Part A). For the expansion it is planned to recruit up to 12 2nd line NSCLC patients. Whether the dose expansion part should be conducted, and how many patients should be enrolled in this expansion will be discussed and agreed by the Safety Review Committee (SRC) according to the available data from Part A.

For the combination regimen dose finding part (Part A), the starting dose will be AZD6244 75 mg (3 x 25 mg capsules). One single oral dose of AZD6244 (75 mg) will be administered on the morning of Day 1, followed by a washout of a minimum of 3 days, and then multiple oral dosing twice daily (75 mg dose in both the morning and evening) in combination with docetaxel (iv 60 mg/m^2 on day 1 of every 21 day cycle). At least 3 evaluable patients will be enrolled in Cohort 1. If this cohort is identified as tolerated by SRC, then it will be escalated to the next cohort.

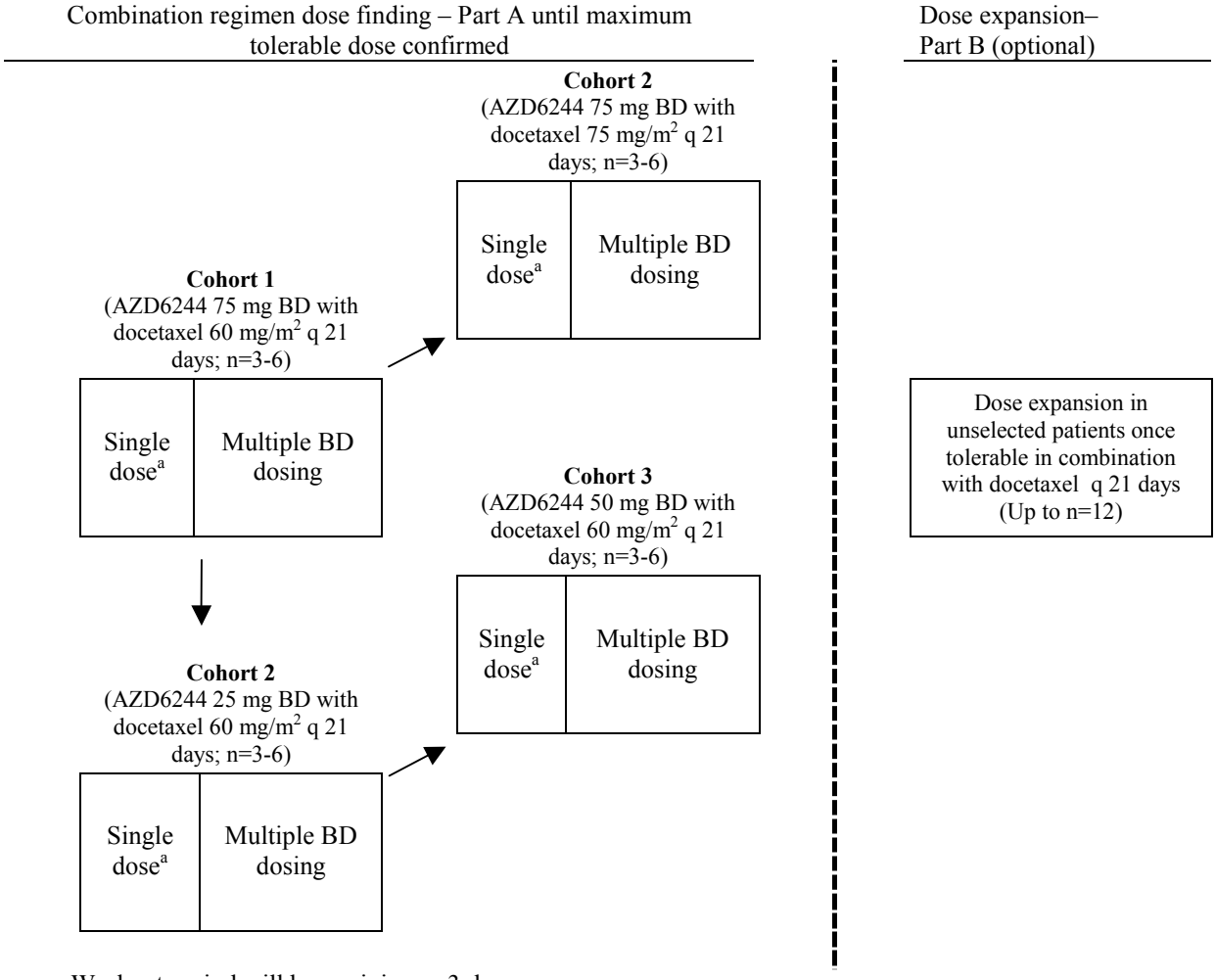
If the Safety Review Committee judge that the dose combination of Cohort 1 is not well tolerated, the study will proceed to a cohort with a lower AZD6244 dose level (Cohort 2).

The single dose period will be defined as Cycle 0, which starts at a single dose on Day 1 until the day before the first dose of multiple dosing in combination with docetaxel. Cycle 1 will be a 21-day period.

The DLT assessment period consists from the first dose of AZD6244 to Day 1/Cycle 2 (docetaxel 2nd dosing). After Cycle 1, patients may continue on Cycle 2, 3, and 4 and onwards of multiple dosing at 21-day intervals.

Patients continuing to tolerate the treatment and receiving any clinical benefit from the treatment may repeat this schedule, until no clinical benefit is apparent (ie, patient has progressive disease), or the patient is withdrawn for other reasons, provided that another written consent on continuous treatment should be obtained from patients before the start of Cycle 2. Patients are expected to receive up to 6 cycles of docetaxel, in the absence of significant toxicity or disease progression. 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.

Figure 1 Flow chart: Combination therapy part



a Washout period will be a minimum 3 days.

3.2 Rationale for conducting this study and for study design

AZD6244 had strong anti-tumour activity in multiple non-clinical models, including human lung cancer tumours (Calu-6), and has been combined with a number of therapeutic agents, including docetaxel using human xenograft models of NSCLC. A beneficial effect of the combination of AZD6244 and docetaxel was observed in a xenograft model (A549a) of *KRAS*-positive NSCLC when compared with either AZD6244 or docetaxel as monotherapy (Haass et al 2008).

The combination of AZD6244 and docetaxel (75 mg/m^2 every 21 days) has been investigated in a Phase I study (D1532C00004) in 35 non-Asian patients with advanced solid tumours (Kim et al 2011, EORTC-AACR abstract). Clinical responses were observed in 5/28 pts (18%) receiving AZD6244 75 mg BD with docetaxel. The recommended Phase II dose of AZD6244 75 mg bd with docetaxel (75 mg/m^2 every 21 days) 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 AZD6244+docetaxel compared with those receiving placebo+docetaxel, and statistically significant improvements in favour of AZD6244 were observed for the secondary endpoints of progression-free survival, objective response rate and patients alive and progression free at 6 months (data on file).

The aim of the combination therapy part of this Phase I combination study (D1532C00067) is to investigate the safety, tolerability and pharmacokinetic profiles of the combination of AZD6244 + docetaxel in Japanese patients receiving it as second line treatment for locally advanced or metastatic NSCLC in order to support the participation of Japanese patients in the forthcoming global Phase III combination study.

The starting dose of the combination therapy in this study is AZD6244 75 mg BD, the dose used in the non-Asian Phase II study (D1532C00016), in combination with docetaxel 60 mg/m^2, the standard Japanese combination dose for docetaxel. If this dose combination is well tolerated, docetaxel 75 mg/m^2, the dose used in the non-Asian Phase II study (D1532C00016), will be investigated in combination with AZD6244 75 mg BD in the next cohort. If this dose combination is not well tolerated, docetaxel may be investigated in combination with the lower dose of AZD6244 in the next cohort.

4. PATIENT SELECTION AND RESTRICTIONS

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

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

4.1 Inclusion criteria

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

1. Provision of written informed consent.

2. Patients must be ≥ 20 years

3. Histological or cytological confirmation of locally advanced or metastatic NSCLC, which is stage IIIB-IV at entry into the study

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 (See Appendix L).

5. Patients will usually have received a platinum-based doublet. However those who received a different 1st line anti-cancer combination regimen or 1st line single agent anti-cancer treatment will be accepted.

6. 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. Radiotherapy alone, radiosensitisers and/or intrapleural administration of anti-cancer agents and adjuvant/neoadjuvant therapy is not counted as a line of therapy.

7. World Health Organisation (WHO) performance status 0-1.

8. Evidence of post-menopausal status or negative urine/serum pregnancy test for non-menopausal female patients.

   Women will be considered postmenopausal if they are amenorrheic for 1 year or more without an alternative medical cause. The following age-specific requirements apply:

   i) Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 1 year or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range.

   ii) Women over 50 years of age would be consider postmenopausal if they have been amenorrheic for 1 year 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).

9. Patients must have calculated creatinine clearance > 50 mL/min using Cockcroft-Gault formula (see Appendix M) or by 24 hour urine collection.

10. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT or MRI and is suitable for repeated assessment.

11. Patients must be able to swallow AZD6244 capsules.

12. Patients must have a life expectancy ≥ 16 weeks.

13. Evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on Cycle 0 Day 1 and every 9 weekly relative to date of Cycle 1 Day 1 (combination start date)

14. Patient is willing to provide a fresh, or archival tumour biopsy.

15. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.

16. Patients can remain in Hospital from Cycle 0/Day 1 (Visit 2) up to at least the completion of Cycle 2/Day 1 (Visit 9).

For inclusion in the optional biomarker research or pharmacogenetic component of the study, patients must provide specific informed consent. If a patient declines to participate in the optional biomarker research or pharmacogenetic component of the study, there will be no penalty to the patient. The patient will not be excluded from the therapeutic study described in this Clinical Study Protocol.

4.2 Exclusion criteria

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

1. Prior treatment with a MEK inhibitor.

2. Prior treatment with docetaxel-containing regimen

3. Previous enrollment or assignment to treatment in the present study.

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

5. Participation in a clinical study during the last 30 days or have not recovered from side effects of an investigational study drug.

6. Recent major surgery within 4 weeks prior to consent (excluding the placement of vascular access) which would prevent administration of standard chemotherapy.

7. Radiotherapy or standard chemotherapy within 21 days prior to entry into the study (not including palliative radiotherapy at focal sites).

8. Brain metastases or spinal cord compression unless treated and stable (for at least 1 month) off steroids.

9. Evidence of active infection or active bleeding diatheses.

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

11. Patients with factors that increase the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome) or QTc interval of > 450 ms for males or > 470 ms for females on screening

12. Evidence of severe or uncontrolled systemic disease (eg, severe hepatic impairment, severe renal impairment uncontrolled diabetes, acute uncontrolled infection) or current unstable or uncompensated respiratory or cardiac conditions and baseline LVEF ≤ 55% or peripheral vascular disease including diabetic vasculopathy, or renal transplant.

13. Patients with documented cases of human immunodeficiency virus (HIV) or active hepatitis B or C infection.

14. Laboratory values as listed below:

    - Absolute Neutrophil Count (ANC) < 1500 per mm^3
    - Platelets < 100000 per mm^3
    - Hemoglobin (Hb) < 9.0 g/dL
    - Serum bilirubin ≥ 1.5 x Upper Limit of Normal (ULN) (known Gilbert's disease excluded)
    - Aspartate aminotransferase (AST/SGOT) or alanine aminotransferase (ALT/SGPT) ≥ 2.5 x ULN or 5 x ULN if liver metastases
    - Patients with proteinuria > 2 gr/24 hr urine collection are excluded

15. Clinical judgment by the Investigator that the patient should not participate in the study.

16. Known hypersensitivity to docetaxel or products containing polysorbate 80.

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

18. Use of strong CYP1A2 or 3A4 inducers and/or inhibitors (for example, but not limited to, ketoconazole, rifampicin, atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit or grapefruit juice, rifabutin, phenytoin, carbamazepine, phenobarbital and St. John's Wort).

4.3 Restrictions

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

1. Reliable methods of contraception should be used consistently and correctly. Some examples of acceptable contraceptive methods are shown below.

   <Barrier method>

   - condom plus spermicide (tablet or jelly, etc.)

   <Other contraceptive methods>

   All the following methods should be used together with a barrier method (condom or spermicide).

   - oral contraceptives
   - intra-uterine device
   - vasectomy of partner

   Preliminary reproductive toxicology data indicate that AZD6244 can have adverse effects on embryo fetal development and survival at dose levels that do not induce maternal toxicity in mice.

   Therefore, patients who are pregnant or actively breast feeding are not eligible to participate in this study. Also female patients of child bearing potential will be required to use reliable methods of contraception for the duration of the study and until 4 weeks after the last dose of study treatment. Male patients will be required to use reliable methods of contraception for the duration of the study and until 6 months after the last dose of AZD6244 treatment.

   The concomitant drug, docetaxel, caused change in testis (atrophy or change in weight) in a study in mice and rats. Also increased in foetal death, development of foetal malformation, delay in development of foetus or newborn were observed when docetaxel was administered to rats before or during pregnancy or after delivery in another study. Therefore, male and female patients should also take precautions to use reliable methods of contraception for 6 months after completion of docetaxel therapy.

Thus both male and female subjects should use acceptable contraceptive methods during the study and for 6 moths after the last dose of AZD6244 and/or the concomitant drug, docetaxel, whichever occurs later.

2. The maximum dose of vitamin E patients may receive from AZD6244 is approximately 210 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided in patients receiving the capsule formulation.

3. Patients who are taking coumadin anticoagulants (eg, warfarin) should have their anticoagulation tested more frequently while taking AZD6244.

4. Throughout the study, patients should avoid changes to or the addition of all concomitant medications, in particular any that are likely to affect the metabolism of AZD6244 (see Section 4.2 Exclusion criteria No.18), unless considered clinically essential for management of concurrent conditions.

5. Grapefruit juice and Seville orange or the juices of these fruits must not be consumed while participating in the study.

6. Patients should avoid excessive sun exposure and use adequate sunscreen protection (SPF45 or higher or PA+++ or higher) if sun exposure is anticipated

7. No food or drink other than water for 2 hours prior to dosing and 1 hour after dosing.

For restrictions relating to concomitant medications see next Section 4.3.1.

4.3.1 Concomitant treatments

- Pre-medication will be allowed after, but not before the first dose of study treatment. This includes management of diarrhoea, nausea and vomiting.

- Blood transfusions are allowed at any time during the study, if clinically indicated to treat anaemia. Blood transfusions should not be used prophylactically during Cycle 1.

- Granulocyte colony stimulating factors support can also be given therapeutically in the first cycle, if clinically indicated to treat neutropaenia (see Section 5.1.5.1). Granulocyte colony stimulating factors should not be used prophylactically during Cycle 1. However use of prophylactic colony stimulating factors may be considered after Cycle 1 following discussion with the AstraZeneca Study Team Physician (see Section 5.1.5.1).

- Throughout the study, patients should avoid changes to, or the addition of all concomitant medications, in particular any that may affect the metabolism of AZD6244 (see Section 4.2 Exclusion criteria No.18), unless considered clinically indicated.

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

- Patients may take warfarin or a coumarin preparation but it is recommended that they should have their anticoagulation monitored carefully and dose adjusted accordingly.

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

- No other standard cancer agents, or investigational drugs should be administered while patients are receiving study medication. Supportive treatments including hormonal and bisphosphonate therapies are allowed.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the CRF. Trade name, generic name, indication, route of administration, dates of administration etc, should be properly documented.

5. STUDY TREATMENT AND CONDUCT

5.1 Treatment

(i) AZD6244

AZD6244 drug product will be provided by AstraZeneca Pharmaceutical Development Supply Chain.

The AZD6244 capsule contains AZD6244 Hydrogen Sulfate equivalent to 25 mg of AZD6244 free base. Capsules are packaged in high-density polyethylene (HDPE) bottles. Additional information about the investigational product may be found in the Investigators' Brochure.

Dosing should not occur until pre-dose blood samples and other study procedures have been completed. AZD6244 will be administered orally in the morning in Cycle 0/ Day 1 and in the morning and evening (twice daily) in Cycle 1/ Day 1 and after. The dose interval should be preferably approximately 12 hours apart and in the fasting condition. The patient should refrain from eating for at least 2 hours pre-dose and 1 hour post-dose (only water will be permitted). In the case of vomiting after taking a tablet and incompliance re-dosing should not be performed.

In the study, following at least 1 cycle of combination therapy, patients may continue to receive AZD6244 in combination with docetaxel until disease progression occurs or as long as they do not experience intolerable toxicity and the investigator believes they are continuing to derive benefit from the therapy.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text will be written by Japanese IPS.

All study drugs should be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified in the document 'Handling Instruction of Investigational Product'.

(ii) Docetaxel

Docetaxel 60 mg/m^2 or 75 mg/m^2 will be administered intravenously on day 1 of every 21 days cycle. Patients are expected to receive up to 6 cycles of docetaxel, in the absence of significant toxicity or disease progression. 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.

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

5.1.1 Starting dose, dose escalation scheme and stopping criteria

5.1.1.1 Part A, Combination regimen dose finding

Patients with confirmed eligibility will be enrolled according to the standard clinical management of their disease.

Dosing will begin at one single oral dose of AZD6244 (75 mg), which will be administered on the morning of Day 1, followed by a washout of minimum 3 days, and then multiple oral dosing twice daily AZD6244 75 mg BD (each in the morning and evening) in combination with docetaxel (iv 60 mg/m^2 on day 1 of every 21 day cycle) will begin (Cohort 1). The single dose period will be defined as Cycle 0, which starts at a single dose on Day 1 until the day before the first dose of multiple dosing. Cycle 1 will be a 21-day period from the first dose of multiple dosing.

1. A minimum of 3 evaluable patients will be enrolled for Cohort 1.

If 0/3 evaluable patients experience a DLT within first cycle of commencing treatment then patients will be enrolled at the next dose level, 75 mg twice daily in combination with docetaxel (iv 75 mg/m^2 on day 1 of every 21 day cycle).

If 1/3 evaluable patients experience a DLT within first cycle of commencing treatment a further 3 patients will be recruited at this dose level (to treat a maximum of 6 patients before further escalation is considered).

Then if;

1/6 evaluable patients experience a DLT, then combination regimen dose will be escalated to the next dose level, 75 mg twice daily in combination with docetaxel (iv 75 mg/m^2 on day 1 of every 21 day cycle)

At any stage if ≥ 2 evaluable patients experience a DLT, recruitment to the cohort will cease and that combination regimen dose will be defined as a non-tolerated dose, and a step to proceed to recruitment to the next Cohort to investigate a lower combination dose will be considered.

2. If combination regimen dose is de-escalated to the next cohort (Cohort 2), a minimum of 3 evaluable patients will be enrolled for Cohort 2, 25 mg twice daily in combination with docetaxel (iv 60 mg/m^2 on day 1 of every 21 day cycle).

If 0/3 evaluable patients experience a DLT within first cycle of commencing treatment then patients will be enrolled at the next dose level, 50 mg twice daily in combination with docetaxel (iv 60 mg/m^2 on day 1 of every 21 day cycle) (Cohort 3).

If 1/3 evaluable patients experience a DLT within first cycle of commencing treatment a further 3 patients will be recruited at this dose level. (to treat a maximum of 6 patients before further escalation is considered.)

At any stage if ≥ 2 evaluable patients experience a DLT, recruitment to the cohort will cease and that combination regimen dose will be defined as a non-tolerated dose.

3. If combination regimen dose is escalated to the next cohort (Cohort 3), a minimum of 3 evaluable patients will be enrolled for Cohort 3, 50 mg twice daily in combination with docetaxel (iv 60 mg/m^2 on day 1 of every 21 day cycle).

If 0/3 or 1/3 evaluable patients experience a DLT within first cycle of commencing treatment then a total of 6 patients will be enrolled in this cohort to confirm the safety and tolerability.

At any stage if ≥ 2 evaluable patients experience a DLT, recruitment to the cohort will cease and that combination regimen dose will be defined as a non-tolerated dose.

Combination regimen dose escalation/decrease decisions will be made jointly, between investigators and AstraZeneca, meeting as a SRC prior to the opening of each cohort. Decisions will follow medical review of available clinical and laboratory data.

There will be no intra-patient dose escalation of AZD6244 or docetaxel this study. If patient experiences an AZD6244 related toxicity, their individual dose may be reduced or withheld at the investigators discretion. All cohort combination regimen dose escalation/reductions will occur in consultation with the SRC. Once a patient has received an AZD6244 dose reduction, there is no provision for re-escalation or re-challenge with a higher dose.

5.1.1.2 Part B, Dose expansion (optional)

If the combination regimen of AZD6244 and docetaxel is determined to be tolerated in Part A, then the dose expansion (Part B) may commence to refine further the safety, tolerability, pharmacokinetics and biological activity at a selected combination regimen uisng the highest

tolerated dose from the escalation (Part A). For the expansion it is planned to recruit up to 12 2nd line NSCLC patients.

Whether the dose expansion phase should be conducted, and how many patients should be enrolled in this expansion will be discussed and agreed by the SRC according to the available data from Part A.

5.1.2 Definition of dose-limiting toxicity (Part A only)

Dose-limiting toxicity (DLT) is defined as any of the following occurrences during the first cycle of single dose until Day 1/Cycle 2 (docetaxel 2nd dosing) of therapy when considered related to docetaxel plus AZD6244 treatment. DLT criteria only apply to combination regimen dose escalation part of study:

Hematologic Toxicities

- Afebrile Grade 4 neutropenia > 5 days or Grade 4 neutropenia associated with fever (reading of body temperature > 38.5°C or 3 readings of body temperature > 38.0°C in a 24-hour period).
- Grade 4 thrombocytopenia
- Inability to resume docetaxel within 14 days of a scheduled administration due to treatment-related toxicity (if the inability to resume docetaxel is felt to be independent of AZD6244 therapy, the adverse event will not constitute a DLT)

Non-Hematologic Toxicities:

- > Grade 3 non-hematological toxicities for > 7 days should be considered a potential DLT that will be finally assessed whether to be definitely DLT or not at the Safety Review Committee. Grade 3 non-hematological toxicities that can be controlled to Grade 2 or less within 7 days with appropriate interruption of treatment with AZD6244 (Section 5.1.5.2) and treatment will not be considered dose limiting. Grade 3 events that do not resolve to CTC grade ≤ 2 events within 7 days despite appropriate treatment interruption and optimal supportive therapy will be considered dose limiting.

If a drug-related DLT should occur after Cycle 1, the course of action to be taken will be decided by consensus of the principal investigators and the sponsor.

For combination regimen dose escalation purposes, only DLT occurring during the first treatment cycle will be considered. However, the incidence and type of DLTs in cycle 2 and beyond will be taken into account in determining combination regimen dose escalation steps. SRC will make decisions regarding combination regimen dose escalation steps.

Combination regimen dose escalation will stop if the defined number of patients in any cohort experiences DLT.

5.1.2.1 Definition of recommended combination dose regimen for Part B

A dose from Part A will be considered non-tolerated if 2 or more of evaluable patients experience a DLT at a combination dose regimen level. If a non-tolerated combination dose regimen is defined in cohort 2, the recommended regimen for Part B dose may be confirmed in cohort 1 at the previous dose level below the non-tolerated combination dose regimen. If cohort 2 combination dose regimen is confirmed to be tolerable in 3 evaluable patients**,** the recommended combination dose regimen for Part B dose will be confirmed at cohort 2 dose regimen in a further 3 evaluable patients. Six evaluable patients are required to determine the recommended dose regimen for Part B.

5.1.3 Definition of evaluable patient

For combination regimen dose escalation decisions, an evaluable patient is defined in principle as a patient who need to have received their first dose of docetaxel and (1) completed at least 75% of planned daily doses of AZD6244 in the first 21 days of multiple dosing period and has enough information to be assessed for the combination regimen dose escalation. If a patient has less than 75% compliance, the patient will not be considered evaluable but will be included in the safety assessment, or (2) experienced a DLT during the first cycle of single dose until Day 1/Cycle 2 (docetaxel 2nd dose); (if the second docetaxel dose was delayed due to bone marrow toxicity, we would have to wait for up to 2 weeks to see if this reached the DLT criteria, hence the evaluation period might extend longer than 21 days up to a potential 35 days.)

Patients withdrawing from treatment for reasons other than (1) or (2) above before completing the evaluation period (up to docetaxel dose in Cycle 2 Day 1) will be replaced.

5.1.4 Safety Review Committee

After completion of a cohort during the combination regimen dose finding phase of the study, a SRC will evaluate the safety and tolerability of AZD6244 in combination with docetaxel to determine the dose levels in the next cohort.

The SRC will consist of:

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

In addition, one other physician from the following may be invited:

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

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

Further internal or external experts may be consulted by the SRC as necessary. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

Once there are at least 3 evaluable patients at a dose level the SRC will review and assess all available safety data from the cohort to make a decision on the dose for the next cohort of patients. Any dose interruptions and reductions will be taken into account.

The decision may be to (refer to Section 5.1.1)

1. Expand the cohort

2. De-escalate and investigate a lower dose of AZD6244 or docetaxel in the next cohort

3. Escalate to investigate a higher dose of AZD6244 or docetaxel in the next cohort

4. Stop the combination regimen dose finding part of the study

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

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

5.1.5 Management of study treatment related toxicity

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.

5.1.5.1 Docetaxel related toxicity

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

Secondary prophylaxis with G-CSF

One of the common side effects associated with docetaxel therapy is reversible bone marrow suppression, often manifesting as severe neutropenia or febrile neutropenia. Secondary G-CSF prophylaxis may be indicated in order to accelerate neutrophil recovery and prevent infectious complications. The investigator should consider administration of G-CSFs on the occurrence of the following adverse events after the first or any other docetaxel infusion in the study:

- Febrile neutropenia, eg, absolute neutrophil count (ANC) < 0.5 x 10^9/L associated with the temperature >38.5°C

- Neutropenia CTCAE grade 4 (ANC < 0.5 x 10^9/L) > 7 days

G-CSF should be administered in line with local practice and ASCO guidelines (Smith et al 2006), usually between 24 to 72 hours after the second and/or subsequent docetaxel infusions. If clinically indicated, G-CSF support can be also given therapeutically in the first cycle following the occurrence of the above events. G-CSF injections (for non-pegylated agents) should continue until the neutrophil count has recovered to > 1.0 x 10^9/L on two consecutive days. Use of G-CSF in subsequent docetaxel treatment cycles will continue at the discretion of the investigator.

It is anticipated that administration of secondary G-CSF prophylaxis will ameliorate the severity of neutropenia and will allow maintaining docetaxel dose at 60 mg/m^2 or 75 mg/m^2, if deemed appropriate by the investigator.

If a patient experiences a new episode of severe neutropenia or febrile neutropenia (as described above) despite G-CSF support, the investigator should consider dose reduction in the subsequent cycles of docetaxel treatment.

Docetaxel dose reduction

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 x 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 the permanently reduced dose from 75 mg/m^2 to 60 mg/m^2 (from 60 mg/m^2 to 45 mg/m^2). Patients must not receive subsequent cycles of docetaxel until ANC recovers to ≥1.5 x 10^9/L and platelets recover to a level of ≥100 x 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. A rechallenge is permitted at the investigator's discretion.

5.1.5.2 AZD6244 related toxicity

Adverse events considered related to administration of AZD6244 are listed in Section 5.4 of the Investigator Brochure. If any adverse events of dyspnoea, asymptomatic decreases in LVEF or diarrhoea occur that are considered at least partly due to administration of AZD6244, algorithms for the investigation and management of these events are provided in Appendices J, K and O respectively. For all adverse events reported in this study that are considered at least partly due to administration of AZD6244 the following dose reduction/adjustment guidance should be applied:

Treatment with AZD6244 should be withheld if one of the following toxicities considered related are observed, despite optimal supportive care:

- Any intolerable adverse event regardless of grade
- Any adverse events ≥ CTCAE Grade 3

AZD6244 treatment may not be restarted until the toxicity improves to CTCAE Grade 1 or baseline, except for rash where patients with CTCAE Grade 2 rash may restart treatment. Additional information on the management of skin toxicity is provided in Section 5.1.5.3 of this protocol.

Treatment may be resumed at the original dose or at a permanently reduced dose at the discretion of the investigator.

If a patient experiences an occurrence of a new toxicity requiring treatment interruption once having restarted on treatment, study medication should again be withheld until the toxicity improves to CTCAE Grade 1 or baseline except for rash where CTCAE Grade 2 rash is acceptable. Upon recovery, treatment may resume at the previous dose level or the dose can be reduced.

However, if a patient experiences recurrence of the same toxicity as that causing a previous dose interruption and/or dose reduction, study medication should be withheld until the toxicity improves to CTCAE Grade 1 or baseline, except for rash where CTCAE Grade 2 rash is acceptable. Upon recovery, treatment should resume at a permanently reduced or adjusted dose.

Dose reduction/adjustment

75 mg twice daily:

- 75 mg once daily, if no dose reduction has yet occurred
- 50 mg twice daily: dose adjustment if dose reduction to 75 mg once daily has already occurred

- 50 mg once daily: dose reduction if dose reduction to 75 mg once daily followed by dose adjustment to 50 mg twice daily has already occurred

- 25 mg twice daily: dose reduction if dose reduction to 75 mg once daily and 50 mg twice daily followed by dose adjustment to 50 mg once daily has already occurred

50 mg twice daily:

- 50 mg once daily, if no dose reduction has yet occurred

- 25 mg twice daily: dose adjustment if dose reduction to 50 mg once daily has already occurred

Once reduced/adjusted, the dose cannot be returned to the previous level.

If a patient experiences recurrence of any toxicity that has already contributed to dose reductions down to the lowest dosing schedule for this study (25 mg twice daily), the patient must discontinue AZD6244 treatment.

If a patient receiving the lowest dosing schedule (25 mg twice daily) experiences a novel toxicity that cannot be adequately managed by dose interruption and medical interventions then the patient must discontinue AZD6244 treatment, as no further dose reductions/adjustments are permitted.

All dose delays, reductions and adjustments will be recorded in the appropriate electronic Case Report Form (eCRF).

Dose re-escalation of AZD6244 is not permitted in this study.

In the event of any dose delay/reduction/adjustment, patients should continue to follow the assessments schedule as described in Table 1 study plan relative to baseline.

5.1.5.3 Algorithm for Management of Skin Toxicity

The aetiology of skin toxicities associated with the use of AZD6244 is uncertain. An algorithm based on dermatology best practices for other contemporary targeted agents that cause skin toxicity (Pérez-Soler et al 2005) is offered as guidance for managing skin toxicities seen in patients being treated on this protocol.

The algorithm suggests a step-wise approach to rash management. If the rash is CTCAE Grade 1, consider starting with topical steroids, topical antibiotics such as clindamycin gel, or no treatment if the patient is asymptomatic. A high potency topical steroid cream, such as clobetasol propionate, may be considered early in patients with mild rash and may be used on the face.

If the rash is CTCAE Grade 2, consider adding an oral tetracycline and/or pimecrolimus cream or similar agent.

If the rash reaches CTCAE Grade 3 or above, dose interruption and/or dose reduction/ adjustment, coupled with the addition of topical steroids is recommended.

Pruritus of any grade may be treated with an antihistamine, such as diphenhydramine or hydroxyzine hydrochloride.

Secondary infection may complicate or worsen skin toxicity. To reduce the likelihood of nasal infection, intranasal mupirocin may be considered. Infected rash may be treated with a short course of an oral tetracycline, such as minocycline hydrochloride. If there is a clinical diagnosis of impetigo, or an infection with Staphylococcus aureus is confirmed, topical mupirocin might be used. Infected lesions suspected to be treatment resistant should be cultured. If there is no improvement after two weeks of treatment, therapy for the rash should be considered ineffective and discontinued. All required treatment information and adverse event information for rash should be recorded on the appropriate CRF.

5.1.6 Duration of therapy

Patients must remain in Hospital from Cycle 0/Day 1 (Visit 2) up to the completion of Cycle 2/Day 1 (Visit 9).

(i) AZD6244

Patients may continue to receive AZD6244 as long as they are continuing to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria (see Section 5.4).

(ii) Docetaxel

Docetaxel will be administered intravenously on day 1 of every 21 day cycle. Patients are expected to receive up to 6 cycles of docetaxel, in the absence of significant toxicity or disease progression. 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.

5.1.7 Treatment compliance and accountability

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca.

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

The unused drugs and empty containers are returned to the AZKK and not destroyed. And the details are shown in 'Handling instruction of Investigational Product' that AZKK provides to sites.

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

5.1.8 Doses and treatment regimens

5.1.8.1 AZD6244 capsule formulation

AZD6244 capsule formulation drug product is supplied as 25 mg capsules in high-density polyethylene (HDPE) bottles.

If patients are not able to tolerate AZD6244, dose reductions are permitted as described in Section 5.1.5.2. Reduced doses will depend on available capsule strengths and the required total daily dose.

Patients will be instructed as to when and how many capsules to use each day.

Study sites will ensure that patients are compliant with treatment.

5.1.8.2 AZD6244 Dosing

Throughout the study no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing. Dosing on a PK day should not occur until pre-dose blood samples and other study procedures have been completed.

The doses should be taken approximately 12 hours apart for example 08:00h and 20:00h or 09:00h and 21:00h.

5.1.8.3 Dosing of AZD6244 in combination with docetaxel

Single dose of AZD6244 will be administered on day 1 of the first cycle (Cycle 0), on Cycle 1/Day 1 twice-daily dose of AZD6244 will be initiated and given continuously on a twice-daily basis. Docetaxel 60 mg/m^2 iv or 75 mg/m^2 iv over 1 hour will be initiated on Cycle 1/Day 1 and given continuously on day 1 of each 21 day cycle.

Please refer to the applicable Product labels for product details and complete instructions regarding administration of docetaxel. For the first cycle of treatment, patients should remain in the treatment area for a minimum of 4 hours following completion of the infusion in the event that acute symptoms, eg, respiratory distress, severe skin reactions, abdominal cramping or diarrhea develop.

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

This study is a Phase I, open-label, dose-finding study. The combination therapy part of this study is designed to investigate the safety, tolerability and pharmacokinetic profile of oral

doses of AZD6244 when administered in combination with docetaxel (iv on day 1 of every 21 day cycle) in 2nd line therapy in Japanese patients with advanced NSCLC.

The starting dose of AZD6244 and docetaxel in the combination therapy part of this study is AZD6244 75 mg BD in combination with docetaxel 60 mg/m^2 which is the standard Japanese combination dose for docetaxel. If this is well tolerated then the dose of docetaxel will be escalated to 75 mg/m^2 which was the MTD of AZD6244 in combination with docetaxel in Phase I (D1532C00004) and the recommended combination dose used in the overseas Phase II 2nd line NSCLC study (D1532C00016). If this dose combination is not well tolerated, docetaxel may be investigated in combination with the lower dose of AZD6244 in the next cohort.

Cohorts of 3 to 6 patients will be recruited during the dose finding phase to allow for early discontinuations and the observation of a minimum of 3 evaluable patients per cohort.

This approach is justified by the fact that the combination regimen dose escalation will commence in the region of pharmacological activity based on the clinical information to date.

The information from this study will be used to determine the doses of AZD6244 and docetaxel when administered in combination in Japanese patients.

5.3 Benefit/risk and ethical assessment

Evidence of AZD6244 anti-tumour activity in advanced NSCLC has been demonstrated in a Phase II monotherapy study (2 partial responses and prolonged stable disease). It is therefore clear that some patients with NSCLC derive benefit from therapy with AZD6244. Further Phase II investigations, utilising AZD6244 both as monotherapy and in combination with other anti-cancer agents, for which there is a strong preclinical rationale, are required to better understand the activity profile of AZD6244.

Phase II study D1532C00016, utilizing AZD6244 in combination with docetaxel, in 2nd line patients with *KRAS* mutation positive NSCLC for which there is a strong preclinical rationale has demonstrated better efficacy and acceptable safety profile of AZD6244 in 2nd line NSCLC (data on file). Based on current information, it is considered that AZD6244 in combination with docetaxel has toxicities that are tolerable/acceptable and sufficient clinical benefit to patients.

Published literature indicates that patients with *KRAS* positive advanced NSCLC do not benefit from adjuvant chemotherapy (Tsao et al 2007) or erlotinib (Eberhard et al 2005). Additionally, recent studies suggest that patients with *KRAS*-mutant tumours are also unlikely to respond to monotherapy with anti-EGFR monoclonal antibodies (cetuximab and panitumumab) (Baselga & Rosen 2008). Such patients represent a low proportion of NSCLC patients and a group with high unmet clinical need due to fewer treatment options available compared to patients whose tumours are *KRAS* wild type. At best the outlook for patients with refractory advanced NSCLC is poor, with a median survival of approximately 6 months at time of failed first treatment.

This study D1532C00067 is therefore designed to investigate the safety profile and tolerability of AZD6244 in combination with docetaxel in Japanese patients with NSCLC in a population that has a similar clinical profile to those studied in Phase II and proposed Phase III in order to support the participation of Japanese patients in the forthcoming global Phase III study of AZD6244 in combination with docetaxel 75 mg/m^2 iv every 21 days in 2nd line NSCLC with *KRAS* mutation positive. The starting dose of AZD6244 and docetaxel in this study is AZD6244 75 mg BD in combination with docetaxel 60 mg/m^2 which is the standard Japanese combination dose for docetaxel. If this is well tolerated then the dose of docetaxel will be escalated to 75 mg/m^2 which was the MTD of AZD6244 Phase I in combination with docetaxel (D1532C00004) and the recommended combination dose used in the overseas Phase II 2nd line NSCLC study (D1532C00016).

In case of any intolerable and severe AEs, the Investigator should follow the instructions provided in Section 5.1.5 and mitigate the risk to a patient by applying suggested dose reduction/adjustment algorithms for AZD6244 and/or adjusting docetaxel dosing, where appropriate.

AstraZeneca believes that the investigation of AZD6244 in combination with docetaxel in the 2nd line advanced NSCLC setting is justified, based on the emerging efficacy data from studies D1532C00004 and D1532C00016 of the combination of AZD6244 with docetaxel.

As a part of this study the patients will undergo standard clinical evaluations, including physical exams, registration of vital signs and basic biometric parameters, safety laboratory evaluations (haematology, chemistry, urinalysis), regular pregnancy tests (where applicable), ECGs, CT/MRI and echocardiogram/MUGA. Diagnostic procedures and assessments mandated by the study protocol were designed with the consideration of safety profiles of both treatments. The types and frequency of assessments are aligned to the current healthcare standards with additional precaution and increase in examinations during the first two 3-weekly cycles of treatment (Cycle 0 and Cycle 1) to ensure timely detection of any early treatment emergent safety signals.

Adverse events related to visual function have been reported at a low frequency in most monotherapy studies with AZD6244. There were no specific clinical findings reported from patients that underwent ophthalmological evaluation after reporting the AE of visual disturbance. To further assess and document any clinical effects that may be linked to development of visual function adverse events in patients receiving AZD6244, a full ophthalmological examination should be conducted at baseline, at Cycle 3 and on the occurrence of any visual disturbance adverse event.

Some patients receiving AZD6244 have been observed to develop asymptomatic decreases in LVEF in the absence of confounding comorbidities. AstraZeneca continues evaluation of LVEF changes in patients receiving AZD6244 and collects baseline and sequential measurements of LVEF and end systolic and diastolic ventricular volumes on echocardiogram/MUGA. As a part of this study, the levels of Troponin I will also be monitored to see if they can help detect any early signs of deterioration of cardiac function.

Given the extensive safety monitoring included in this study, and inclusion of a full review of available safety, tolerability and pharmacokinetic data prior to each combination regimen dose escalation decision, AstraZeneca believes that the overall risk for the patients who participate in this study would be acceptable.

5.4 Discontinuation of investigational product and withdrawal from study

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

- Patient decision. The patient is at any time free to withdraw his/her participation in the study, without prejudice
- Safety reasons as judged by the investigator and/or AstraZeneca
- Adverse events
- Severe non-compliance to this protocol as judged by the investigator and/or AstraZeneca
- Confirmed disease progression
- Patients incorrectly initiated on investigational product and docetaxel (Section 5.4.1)
- Patient becomes pregnant
- Patient lost to follow-up

Any patient who permanently discontinues investigational product and docetaxel will be withdrawn from the study (Section 5.4.2).

Patients that are withdrawn from the study but are evaluable per the definition in Section 5.1.3 will not be replaced. Any patient that is withdrawn and is not evaluable will be replaced to ensure a minimum number of evaluable patients.

Patients may withdraw from any aspects of the voluntary exploratory research (see Section 16) at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Section 17.5.

5.4.1 Procedures for handling patients incorrectly initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be initiated on investigational product and docetaxel. There can be no exceptions to this rule.

Where patients start the study treatment in error eg, where patients are subsequently identified as having failed to meet the inclusion/exclusion criteria, the procedures included in the protocol for the discontinuation of such patients must be followed (see Section 5.4.2).

5.4.2 Procedures for withdrawal from study

A patient that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The Principal Investigator/Sub-Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. They will also immediately inform AstraZeneca of the withdrawal. Adverse events should be followed up (see Sections 13.3 and 13.4) and study drug should be returned by the patient.

5.5 Study timetable and end of study

The end of this study is defined as the date of the last visit of the last patient, occurring when all patients have completed study therapy.

Planned duration of the study:

Study period: April, 2012 - June, 2014

Registration period: April, 2012 – January, 2014

There will be a data cut-off defined as the earlier of 6 months after the last patient recruited starts investigational product and docetaxel or follow up visit at 28 days after the final patient discontinues investigational product. Data analysis will be performed and a Clinical Study Report written based on this data set.

Any patients still continuing on the study at the time of this data cut-off will be able to continue to receive AZD6244 and docetaxel while deriving clinical benefit. Such patients will continue to be monitored up to 28 days after the last dose of investigational product and docetaxel. A Clinical Study Report Addendum will be prepared to summarise the additional safety data collected between the data cut-off and the end of the study.

6. STUDY PLAN AND COLLECTION OF STUDY VARIABLES

6.1 Study Plan

Table 1 Study plan (Combination Therapy Part)

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14+** [a]	Discontinuation from treatment	
Visit Description	Screening	Treatment Period													Treatment Discontinuation Visit	28 days post last dose of last study treatment
Cycle		0				1			2			3	4	5		
Day	-14 to –1	1	2	3	4	1	8	15	1	8	15	1	1	1	N/A	N/A
Visit Window (compared to Day 1)	N/A	N/A				* [b]	±2 days	±2 days	±2 days	±2 days	±2 days	±1 wk	±1 wk	±1 wk	N/A	±7 days (compared to trt disc visit)
Main study informed consent	X								X[c]							
Demography (date of birth, sex, race)	X															
Patient background (histology, disease staging, medical and surgical history, concomitant disease, previous cancer therapy, smoking status)	X															
Archival tumour sample-original archival diagnostic or more recent (pre-study) archival biopsy [d]	X															
Optional at progression fresh biopsy [d]															(X)	
Optional blood sample for genetic research [f]		(X)														
Optional blood sample for biomarker analysis [g]	(X)					(X)	(X)		(X)			(X)		(X)	(X)	
Adverse events [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [h]
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1 Study plan (Combination Therapy Part)

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14+** [a]	Discontinuation from treatment	
Visit Description	Screening	Treatment Period													Treatment Discontinuation Visit	28 days post last dose of last study treatment
Cycle		0				1			2			3	4	5		
Day	-14 to –1	1	2	3	4	1	8	15	1	8	15	1	1	1	N/A	N/A
Visit Window (compared to Day 1)	N/A	N/A				* [b]	±2 days	±2 days	±2 days	±2 days	±2 days	±1 wk	±1 wk	±1 wk	N/A	±7 days (compared to trt disc visit)
Vital signs (resting blood pressure, pulse rate, body temperature) including weight and height [e]	X [e]	X	X			X	X	X	X			X [i]	X	X [i]	X	(X) [j]
Clinical chemistry/haematology	X	X	X			X	X	X	X	X [k]	X [k]	X	X	X	X	(X) [l]
Urinalysis [m]	X	X	X			X	X	X	X			X	X	X	X	
Pregnancy test (pre-menopausal females only)	X	X											X			
PK blood sampling for AZD6244 [n]		X	X	X	X	X	X									
PK blood sampling for docetaxel [n]						X										
Troponin I	X											X		X		
ECG [o]	X	X				X			X			X [i]		X [i]	X	(X) [j]
WHO performance status	X								X			X	X	X	X	
Echocardiogram/MUGA [i]	X [p]											X		X		(X) [j]

Table 1 Study plan (Combination Therapy Part)

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14+** [a]	Discontinuation from treatment	
Visit Description	Screening	Treatment Period													Treatment Discontinuation Visit	28 days post last dose of last study treatment
Cycle		0				1			2			3	4	5		
Day	-14 to –1	1	2	3	4	1	8	15	1	8	15	1	1	1	N/A	N/A
Visit Window (compared to Day 1)	N/A	N/A				* [b]	±2 days	±2 days	±2 days	±2 days	±2 days	±1 wk	±1 wk	±1 wk	N/A	±7 days (compared to trt disc visit)
Tumour evaluation by RECIST [q]	X [r]											X		X	X	
Physical examination	X [s]								X [s]			X	X	X	X	
Ophthmalmologic examination [t]	X											X				(X) [j]
AZD6244 dosing [u]		X Single dosing	(wash-out)			twice-daily dosing →										
Docetaxel infusion						X			X			X	X	X [v]		
Check returned study medication									X			X	X	X	X	

a From Visit 14 onwards patients to attend clinic visits every 3 weeks until discontinuation of treatment with assessments matching those at visit 14, with the exception of Troponin I (not assessed at any further scheduled visits, only assessed on occurrence of any cardiorespiratory event with no obvious diagnosis), RECIST assessments (see Section 18.1), echocardiogram(MUGA)/single ECG (every 12 weeks), pregnancy test (every 9 weeks from Visit 13) and physical examination (whilst patients are receiving docetaxel [with or without AZD6244] physical examination to be performed every 3 weeks; for patients who have stopped docetaxel and are receiving only AZD6244, physical examination to be performed every 9 weeks).

b To schedule the visit date for Visit 7 or thereafter based on the starting date of Cycle 1.

c Another informed consent should be obtained from patients before the start of Cycle 2 (see Section 3.1).

d The tumour sample collected can be the original diagnostic tumour specimen, or a more recent archival tumour specimen collected pre-study. Optional fresh biopsy will be taken at the time of documented progression.

e Height will be measured only at screening.

f **Consenting patients only (separate consent required for genetic analysis).** If a patient agrees to participate in the host pharmacogenetics research component of the study (by signing the optional Pharmacogenetics research consent), a 10 mL blood sample will be collected. This should be taken once the patient has been enrolled into treatment. Since DNA is a stable parameter, this sample may be taken at other times on the study.

g **Optional biomarker blood sample (separate biomarker consent required prior to taking sample).** Blood samples (1 x 4 mL and 1 x 10 mL) will be taken to provide serum and plasma respectively at each time-point. The blood samples will be taken at screening, pre-treatment on Day 1, Day 8 of Cycle 1, Day 1 of Cycle 2, Day 1 of Cycle 3, pre-dose Day 1 of alternate other cycle and at discontinuation of therapy.

h All cardiorespiratory AEs with no obvious diagnosis should be assessed with an echocardiogram/MUGA, single ECG, vital signs, weight and blood samples for Troponin I taken at the time of the event. Asymptomatic decreases in LVEF should be investigated according to the algorithm provided in Appendix K. All new dyspnoea AEs or worsening of pre-existing dyspnoea AEs should be followed up according to the dyspnoea algorithm provided in Appendix J. If a patient experiences an AE of visual disturbance (including blurring of vision) a complete full ophthalmological examination, including a slit-lamp examination, must be performed (see Section 6.3.11.4).

i Vital signs (including weight) and single ECG must be repeated each time an echocardiogram/MUGA is performed and as described in footnote h. These assessments should not be repeated during the relevant visit if already performed as part of the echocardiogram/MUGA procedure.

j Patients who have a drop in LVEF >10% percentage points from baseline at time of discontinuation of AZD6244 should have a follow up echocardiogram/MUGA, single ECG and vital signs (including weight) performed 28 days after discontinuation of AZD6244 in order to document reversibility. Patients who have a retinal abnormality prior to discontinuation of AZD6244 should, if practicable, have a follow up eye examination performed 28 days after discontinuation of AZD6244 in order to document reversibility (See Section 6.3.6).

k Haematology samples only to be collected 7 days and 14 days after the second infusion of docetaxel.

l All patients with an AST, ALT or bilirubin value > ULN at time of the last dose of AZD6244 should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 28 days (±7 days) after permanent discontinuation of AZD6244.

m For urinalysis, a single-spot early morning urine specimen will be collected on the day of the scheduled visit, where the local laboratory is able to determine urine albumin and urine creatinine concentrations from a single-spot urine specimen.

n Blood samples for AZD6244 PK to be collected on Cycle 0/Day 1, Day 2, Day 3 and Day 4, and Cycle 1/Day 1 and Day 8. Blood samples for docetaxel PK will be collected on Cycle 1/Day 1. See Table 2 for complete schedule.

o Single ECG at Visit 1, treatment discontinuation visit and each time an echocardiogram/MUGA is performed; triplicate ECGs pre-dose, 2 hours and 4 hours post-dose of AZD6244 at Visit 2 and Visit 6, and 2 hours post-dose of AZD6244 at Visit 9.

p Baseline echocardiogram/MUGA can be performed up to 28 days prior to enrolment.

q RECIST assessment will be performed using CT or MRI scans of chest and abdomen, including liver and adrenal glands. Any other areas of the disease involvement should be additionally investigated based on signs and symptoms of individual patients. Follow-up assessments will be performed at week 6 (±1 week), week 12 (±1 week), week 18 (±1 week), week 24 (±1 week), then every 12 weeks (±1 week), and treatment discontinuation relative to start of study treatment until objective disease progression by RECIST 1.1. Any other sites at which new disease is suspected should also be appropriately imaged.

r Baseline CT or MRI scans can be performed up to 28 days prior to start of study treatment.

s Physical examination to occur every 3 weeks whilst patient receives docetaxel + AZD6244, and every 9 weeks (relevant to Day 1) after chemotherapy with docetaxel is completed and the patient continues to receive AZD6244 only.

t Full ophthalmological examination should include a slit-lamp examination (see Section 6.3.11.4).

u Patients will receive AZD6244 for as long as, in the opinion of the investigator, they are receiving clinical benefit in the absence of significant toxicity. AZD6244 treatment should continue after docetaxel treatment has finished. Patients should continue to receive AZD6244 until at least RECIST defined progression.

- Patients are expected to receive up to 6 cycles of docetaxel, in the absence of significant toxicity or disease progression. 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.

Table 2 PK sample collection AZD6244 and docetaxel

Study Day	Time	AZD6244	Time	Docetaxel
C0/ D1	Pre-dose (within 10 minutes prior to dosing)	X		
	30 min[a]	X		
	1 h[a]	X		
	1 h and 30 min[a]	X		
	2 h[a]	X		
	4 h[a]	X		
	8 h[a]	X		
	12 h[a]	X		
C0/ D2	24 h[a]	X		
C0/ D3	48 h[a]	X		
C0/ D4	72hr[a]	X		
C1/ D1	Pre-dose (within 10 minutes prior to dosing)	X	Pre-infusion	X
	30 min[a]	X	30 min[b]	X
	1 h[a]	X	End/1 h[b]	X
	1 h and 30 min[a]	X	1 h and 30 min[b]	X
	2 h[a]	X	2 h[b]	X
	4 h[a]	X	4 h[b]	X
	8 h[a]	X	8 h[b]	X
	12 h[a]	X	12 h[b]	X
C1/ D8	Pre-dose (within 10 minutes prior to dosing)	X		
	30 min[a]	X		
	1 h[a]	X		
	1 h and 30 min[a]	X		
	2 h[a]	X		
	4 h[a]	X		
	8 h[a]	X		
	12 h[a]	X		

a Relative to time of dose of AZD6244
b Relative to start of infusion

6.2 Recording of data

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

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and for the provision of answers to data queries according to the applicable information.

The investigator will sign the completed Case Report Forms. A copy of the completed Case Report Forms will be archived at the study site.

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

The investigator will record data on the observations, tests and assessments specified in the protocol on the electronic CRFs provided by AstraZeneca. The CRF will be accompanied with 'Instructions for the investigator', which should be followed. These instructions provide guidance for the recording of study data in the CRF including how to change data incorrectly recorded.

6.3 Safety procedures

The primary study variable is safety. The following study measurements will be obtained at various time points throughout the study. The times of these measurements are detailed in the study plans (Section 6.1).

- ECG
- Vital signs (including weight)
- Physical examination
- Safety assessments (clinical chemistry, hematology, urinalysis, etc)
- Echocardiogram/MUGA
- Troponin I
- Ophthalmologic examination

6.3.1 Enrollment and screening (Visit 1)

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

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

The registration centre manages and keeps the registration code centrally and electronically. The name and contact of centre are as follows:

Name: AZD6244 Registration Centre

Office hours: 9:30 - 17:30, Mon - Fri

(Closed on Sat and Sun, national holidays, 29 Dec - 4 Jan)

E-code (EXXXXYYY) consists of a 4-digit centre number (XXXX) and a 3-digit serial number (YYY, starting with 001) issued by each study centre in order of informed consent taken. For centre number, see Supplement A "Investigators and Study Administrative Structure".

The investigator(s) fill in the "Enrolment Notification Form" after the written informed consent is obtained, and send the form to the AZD6244 Registration Centre by fax. The registration centre records the information on the enrolment list which is maintained in registration centre and sends the "Enrolment Confirmation Form" to the investigator(s) by fax.

The investigator(s) send the "Registration Notification Form" to the registration centre by fax (both eligible and ineligible) after confirming of the patient's eligibility. The registration centre confirms the patient eligibility and sends the "Registration Confirmation Form" to the investigator(s) by fax with the registration number when the patient is eligible.

The registration number is a 3-digit serial number, ie, starting with the following numbers for each dose.

Cohort	Registration number
1	101, 102, 103…
2	201, 202, 203…
3	301, 302, 303...
4	401, 402, 403...

If a patient is not evaluable for the dose escalation, an additional patient could be entered in that dose level.

Each patient will undergo screening (see Study Plan Table 1) during the 14 days prior to admission to confirm eligibility (see Sections 4.1 and 4.2). Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided

the assessments fall within the protocol specified period prior to the first dose of study treatment. Once all criteria for eligibility have been checked, and the patient fulfils all the inclusion and none of the exclusion criteria, the patient is then eligible to receive AZD6244.

The screening will consist of:

- Demography (date of birth, sex, race)
- Collection of AEs will start after signing the first consent form.
- Main study informed consent will be obtained prior to all other study procedures including consent for access to the original archival diagnostic tumour or a more recent archival biopsy.
- Optional consent for blood samples for biomarker analysis, and optional consent for a fresh biopsy to be taken at documented progression of the patient.
- Optional consent for blood sample for pharmacogenetics.
- The following patient background information will be collected for each patient:
  - Histological/cytological confirmation of NSCLC
  - Disease staging
  - Medical and surgical history, concomitant disease
  - Concomitant medications and previous anti-cancer therapy
  - Smoking status
- Tumour evaluation according to RECIST 1.1. guidelines using CT or MRI of the chest and abdomen including liver and adrenal glands must have been performed up to 28 days prior to first study treatment. Any other areas of the disease involvement should be additionally investigated based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 4 weeks before start of treatment
- Assessment of WHO performance status
- Physical Examination
- Vital signs (resting blood pressure (BP), pulse rate, body temperature), weight and height
- Blood samples for clinical chemistry and haematology

- Blood samples for Troponin I
- Blood samples for biomarker analysis (optional)
- Urinalysis
- Pregnancy test for female pre-menopausal patients
- Single ECG
- Full ophthalmologic examination, including slit-lamp examination
- Echocardiogram (can have been performed up to 28 days prior to first study treatment)/MUGA
- For those patients who agree to have original archival diagnostic tumour or a more recent archival biopsy, informed consent will be obtained and a pre-dose tumour sample collected. (for details see Appendix I)

6.3.2 Visit 2, Cycle 0 Day 1

During this visit eligible patients will be enrolled into the study to commence treatment with AZD6244 single dosing.

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

Prior to dosing the patients will undergo the following assessments and procedures:

- Collection of AEs
- Changes to concomitant medications
- Vital signs (resting BP, pulse rate, body temperature) and weight
- Triplicate ECGs (within 5 mins) pre-dose, 2 hours and 4 hours post-dose of AZD6244
- Pre-dose PK sample (within 10 minutes prior to dosing) with subsequent samples taken at 0.5, 1, 1.5, 2, 4, 8 and 12 hours post-dose of AZD6244
- Blood samples for clinical chemistry and haematology
- Urinalysis
- Pregnancy test for female pre-menopausal patients

- For those patients who agree to have a blood sample stored for future host genetic analysis, host genetics research informed consent will be obtained and a pre-dose blood sample collected (for details see Appendix H)

- AZD6244 single dosing will be administered orally to all patients on Visit 2, Cycle 0 Day 1.

6.3.3 Follow-up visits (Visit 3, Cycle 0 Day 2 – onwards until discontinuation)

- Patients will attend follow-up visits. At each of these visits patients will undergo the following assessments:

- Collection of AEs. Please note:

  – All cardiorespiratory AEs with no obvious diagnosis should be assessed with an echocardiogram/MUGA, single ECG, vital signs (resting BP, pulse rate, body temperature), weight and blood samples for Troponin I taken at the time of the event

  – Asymptomatic decreases in left ventricular ejection fraction (LVEF) should be investigated according to the algorithm provided in Appendix K

  – All new dyspnoea AEs or worsening of pre-existing dyspnoea AEs should be followed up according to the dyspnoea algorithm provided in Appendix J

  – If a patient experiences an AE of any visual disturbance (including blurring of vision) a complete ophthalmologic examination, including slit-lamp examination, must be performed.

- Changes to concomitant medications

- Blood samples for clinical chemistry and haematology on Cycle 0 Day2, Cycle 1 Day 1, Day 8 and Day 15, Cycle 2 Day1 and every 3 weeks thereafter. Note: only haematology samples must be collected 7 days and 14 days after the second infusion of docetaxel (Cycle 2 Day 8 & Day 15).

- Blood samples for biomarker analysis (optional) will be taken at pre-dose on Day 1, Day 8 of Cycle 1, Day 1 of Cycle 2, Day 1 of Cycle 3 and pre-dose Day 1 of alternate other cycle.

- To all patients, on cycle 1 Day 1 (Visit 6) twice-daily dose of AZD6244 will be initiated and given continuously on a twice daily basis. Docetaxel will start to be administered intravenously to all patients on Cycle 1 Day 1 (Visit 6), and given continuously on day 1 of each 21 day cycle.

Additional assessments will be performed as follows:

- RECIST evaluations using CT (or MRI) of chest and abdomen (including liver and adrenal glands) to be performed at week 6, week 12, week 18, week 24, and every 12 weeks thereafter relative to date of Cycle 1 Day 1 (combination start date).

- Vitals signs (resting BP, pulse rate, body temperature) and weight on Cycle 0 Day 2 and Cycle 1 Day 1, Day 8, Day 15, Cycle 2 Day 1 and every 3 weeks thereafter (please note that vital signs should not be repeated if they have already been taken at the time of the echocardiogram at the same visit)

- Urinalysis on Cycle 0 Day 2, Cycle 1 Day 1, 8, 15, Cycle 2 Day 1 and every 3 weeks thereafter

- Triplicate ECGs (within 5 mins) pre-dose, 2 hours and 4 hours post-dose of AZD6244 on Cycle 1 Day 1, and 2 hours post-dose of AZD6244 Cycle 2 Day 1. Single ECG on Cycle 3 Day 1, Cycle 5 Day 1 and every 12 weeks thereafter will also be recorded at the time of every echocardiogram assessment.

- PK blood sampling for AZD6244 (during Cycle 0): Subsequent PK samples taken at 24 hours, 48 hours, 72 hours post-single dose of AZD6244 on Cycle 0 Day 1.

- PK blood sampling for AZD6244 (Cycle 1): Pre-dose PK sample (within 10 minutes prior to dosing) with subsequent samples taken at 0.5, 1, 1.5, 2, 4, 8 and 12 hours post-dose of AZD6244 on Cycle1 Day 1 and Cycle 1 Day 8. Patients must withhold taking the morning dose of AZD6244 until pre-dose PK sample is collected.

- PK blood sampling for docetaxel (Cycle 1): Pre-dose PK sample (pre-infusion) with subsequent samples taken at 0.5, 1, 1.5, 2, 4, 8 and 12 hours post-starting infusion of docetaxel on Cycle1 Day 1.

- Assessment of WHO performance status on Cycle 2 Day 1, Cycle 3 Day 1 and at every scheduled visit thereafter

- Patients are expected to receive up to 6 cycles of docetaxel administered intravenously on day 1 of every 21 day cycle, in the absence of significant toxicity or disease progression. 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.

- Check AZD6244 returned medication on Cycle 2 Day 1 and at every scheduled visit thereafter

- Echocardiogram/MUGA on Cycle 3 Day 1, Cycle 5 Day 1 and every 12 weeks thereafter, and treatment discontinuation. Vital signs (resting BP, pulse rate, body

temperature) and weight and a single ECG must also be recorded at the time of every echocardiogram assessment.

- A full ophthalmologic examination will be performed on Cycle 3 Day 1 and on occurrence of any AE of any visual disturbance (including blurring of vision)

- Blood samples for Troponin I will be taken on Cycle 3 Day 1 and Cycle 5 Day 1, and on occurrence of any cardiorespiratory event with no obvious diagnosis

- Physical examination will be performed every 3 weeks whilst patients are receiving docetaxel + AZD6244. Following completion of docetaxel therapy, whilst patients continue to receive only AZD6244, the frequency of physical examinations will reduce to once every 9 weeks relevant to Day 1 of the study (eg, week 9, week 18 and every 9 weeks relative to date of Cycle 1 Day 1 (combination start date) thereafter).

- Pregnancy test for female pre-menopausal patients performed on Cycle 4 Day 1 and every 9 weeks thereafter.

Patients will be permitted to continue to receive any study treatment after objective disease progression if, in the opinion of the investigator, they are continuing to derive clinical benefit from study treatment, in the absence of significant toxicity.

6.3.4 Treatment discontinuation visit

The treatment discontinuation visit will be conducted as soon as possible after the patient received the last dose of study drug. This will either be after the last dose of AZD6244 or docetaxel, depending on which treatment is discontinued last.

During this visit patients will undergo the following assessments:

- RECIST evaluations using CT (or MRI) of chest and abdomen (including liver and adrenal glands)

- Assessment of WHO performance status

- Vital signs, (resting BP, pulse rate, body temperature) and weight

- Physical examination

- Blood samples for clinical chemistry and haematology

- Blood samples for biomarker analysis (optional)

- Urinalysis

- Single ECG

- Collection of AEs
- Changes to concomitant medications
- Check AZD6244 returned medication
- Collection of optional fresh tumor samples

Following discontinuation of AZD6244 and docetaxel for any reason, patients may receive any subsequent therapy for NSCLC at the discretion of the investigator. Details of such treatment (including surgery) are to be recorded in the eCRF.

Collection of AEs/SAEs will continue until 28 days after the last dose of the last study treatment. 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 eCRF.

6.3.5 28 days after last dose of last study treatment

Twenty-eight (28) days (±7 days) after permanent discontinuation of the study treatment (AZD6244) or docetaxel a treatment discontinuation follow-up contact should be performed to collect the following for all patients:

- AEs
- Changes to concomitant medications (following this visit, only anti-cancer treatment [including surgery] will be collected).

6.3.6 Additional assessments 28 days after last dose of AZD6244

Twenty-eight (28) days (±7 days) after the last dose of AZD6244 has been taken, the following assessments should be performed, where necessary:

- All patients with an AST, ALT or bilirubin value above upper limit of normal (ULN) at time of the last dose of AZD6244 should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed.
  NB. In case a patient shows an AST or ALT ≥ 3 x ULN or total bilirubin ≥ 2 x ULN please refer to Appendix N 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law' for further instructions.
- Patients who have a drop in LVEF >10% percentage points from baseline at time of discontinuation of AZD6244 should have a follow up echocardiogram/MUGA, single ECG and vital signs (include weight) performed in order to document reversibility.

- Patients who have a retinal abnormality prior to discontinuation of AZD6244 should, if practicable, have a follow up eye examination performed 28 days after discontinuation of AZD6244 in order to document reversibility.

When AZD6244 is the last study drug to be discontinued, these assessments should be performed in addition to the assessments described in Section 6.3.5.

If AZD6244 is discontinued before docetaxel, these assessments should be performed 28 days (±7 days) after the last dose of AZD6244. The assessments described in Section 6.3.5 should then be performed 28 days after docetaxel is permanently discontinued.

6.3.7 Laboratory safety assessment

The following clinical chemistry, haematology and urinalysis tests will be performed:

Table 3 Laboratory safety assessments (Combination Therapy Part)

Clinical chemistry	Haematology	Urinalysis [a]
s-Albumin	Erythrocyte count	u-Albumin
s-ALT	Haemoglobin	u-Creatinine
s-AST	Platelet count	
s-ALP	Leucocyte cell count	
s-Total Calcium	Leucocyte differential count (absolute count):	
s-Creatinine	Neutrophils	
s-Gamma glutamyl transferase (γGT)	Eosinophils	
s-Glucose	Basophils	
s-Magnesium	Lymphocytes	
s-Phosphate	Monocytes	
s-Potassium		
s-Sodium		
s-Total protein		
s-Total bilirubin		
s-Urea nitrogen		
s-Troponin I		

a To be performed at sites where the local laboratory is able to determine urine albumin and urine creatinine concentrations from a single-spot specimen
s serum
u urine

All the laboratory safety assessments will be analysed by the local laboratory.

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

For blood volume see Section 17.1.

A single-spot early morning urine specimen will be collected on the day of scheduled visit., at sites where the local laboratory is able to determine the concentration of urine albumin and urine creatinine from a single-spot urine specimen. Investigational sites unable to report these parameters will perform routine urinalysis according to the local standard of care.

6.3.8 Physical examination

A physical examination will be performed at screening and every 3 weeks whilst patients are receiving docetaxel + AZD6244. Following completion of docetaxel therapy, whilst patients continue to receive only AZD6244, the frequency of physical examinations will reduce to once every 9 weeks, relevant to Day 1 of the study (eg, week 9, week 18 and every 9 weeks relative to date of Cycle 1 Day 1 (combination start date) thereafter.

The last physical examination in the study will be performed at treatment discontinuation visit.

6.3.9 ECG

ECGs will be analysed locally. Patients should be supine and at rest 10 minutes prior to recording the ECG.

Parameters including heart rate, duration of QRS complex, R-R, PR and QT intervals will be collected. QTcF will be calculated by AstraZeneca from the data provided.

The investigator should review the paper copy of the ECGs on each study day and may refer to a local cardiologist if appropriate.

Any symptoms from the patient should be registered as a comment and if AE criteria are met, recorded as an AE.

6.3.9.1 Screening ECG

At screening all patients will have a single 12-lead ECG performed. The screening ECG can be conducted up to 14 days prior to Cycle 0 Day 1.

6.3.9.2 Treatment Phase ECGs

Patients will have 12-lead ECGs captured in triplicate (within 5 mins) pre-dose, 2 hours and 4 hours post-dose of AZD6244 on Cycle 0 Day 1, Cycle 1 Day 1 and 2 hours post-dose of AZD6244 on Cycle 2 Day 1. Single ECGs must also be performed at the time of every echocardiogram assessment and on occurrence of any cardiorespiratory adverse event. A single ECG is also required at discontinuation of treatment.

6.3.10 Vital signs

Resting blood pressure and pulse rate will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size. Vital sign assessments, including weight, will be performed at screening, Cycle 0 Day 1, Cycle 0 Day 2, Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1 and then 3 weekly thereafter, at discontinuation of the last study treatment, and at the time of any echocardiogram assessment. Height will be assessed at screening only.

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

6.3.11 Other safety assessments

6.3.11.1 Pregnancy test

A pregnancy test will be performed at screening, prior to starting treatment at Cycle 0 Day 1, from thereafter at Cycle 4 Day 1 and 9 weekly thereafter for female pre-menopausal patients.

6.3.11.2 Echocardiogram/MUGA

An echocardiogram will be conducted at screening (can have been performed up to 28 days prior to first study treatment) and on Cycle 3 Day 1, Cycle 5 Day 1 and at 12 weekly intervals on treatment. A further echocardiogram should be performed as part of the assessment package for any cardiorespiratory adverse event with no obvious diagnosis (eg, not mandated in case of confirmed pulmonary embolus or myocardial infarction).

Left ventricular ejection fraction (LVEF), end diastolic and end systolic left ventricular diameters should be recorded at each echocardiogram assessment. Patients experiencing an asymptomatic but clinically significant drop in LVEF should be managed according to the algorithm provided in Appendix K. Patients who have a drop in LVEF >10% percentage points from baseline at time of discontinuation of AZD6244 should have a follow-up echocardiogram performed 28 days after permanent discontinuation of AZD6244 in order to document reversibility.

6.3.11.3 Troponin I

Blood samples for Troponin I will be collected at screening and on Cycle 3 Day 1, Cycle 5 Day 1 and in cases of any cardiorespiratory AEs with no obvious diagnosis and will be sent to a laboratory for analysis.

6.3.11.4 Ophthalmologic examination

A complete ophthalmologic examination including a slit-lamp examination must be performed at screening, on Cycle 3 Day 1 and when a patient experiences a visual disturbance AE (including blurring of vision). The ophthalmologic examination will include assessment of visual acuity, a slit lamp examination, measurement of intraocular pressure and funduscopy.

Monotherapy Part: Sections From 7 to 12

7. STUDY OBJECTIVES (MONOTHERAPY PART)

7.1 Primary objective

To investigate the safety and tolerability of oral doses of AZD6244 when administered as a monotherapy in Japanese patients with advanced solid malignancies.

7.2 Secondary objective(s)

To evaluate the pharmacokinetics of AZD6244.

7.3 Exploratory objective(s)

To define the recommended dose for future studies of AZD6244 in Japanese patients.

To analyse biological samples (eg, biopsy, archived tumor, serum/plasma) for factors, which may influence the response to AZD6244, such as genetic variability, gene expression profile, protein expression profile etc.

To collect a blood sample for DNA extraction and storage to provide data to investigate whether variability in the PK, safety, or efficacy results could be explained by differences in the patient's genotype or phenotype.

To make a preliminary assessment of tumor response as measured by Objective Response Rate (ORR) per investigators assessment using RECIST 1.1 when AZD6244 is given as a monotherapy in Japanese patients with advanced solid malignancies.

8. BACKGROUND

8.1 Mitogen activated protein kinase (MEK)

Refer to section 2.2 of the Combination therapy part.

8.2 AZD6244 (selumetinib)

Refer to section 2.3 of the Combination therapy part.

8.3 Non-clinical information and correlative studies

8.3.1 Pre-clinical experience with AZD6244

Refer to section 2.4.1 of the Combination therapy part.

8.3.2 Clinical experience

Clinical experience with AZD6244 as monotherapy and in combination with other anti-cancer agents is described in the current version of the AZD6244 Investigator's Brochure. Clinical experience with AZD6244 monotherapy is summarised below.

The final safety data from a study of AZD6244 monotherapy in Phase I oncology populations (patients with advanced solid malignancies): a dose escalation study of AZD6244 Hyd-Sulfate capsules (D1532C00005) are summarised below.

DLTs were recorded in 3 patients during their first 22 days of treatment with AZD6244 Hyd-Sulfate capsules. Two patients in the 100 mg bd cohort experienced a DLT (1 patient had Grade 3 rash and 1 patient had Grade 3 pleural effusion), and the dose was designated to be non-tolerated; 1 patient in the 75 mg bd cohort experienced a DLT of Grade 3 fatigue. The 75 mg bd dose was determined to be the MTD of the AZD6244 Hyd-Sulfate capsule formulation.

The most frequently reported AEs in the AZD6244 75 mg bd cohort were fatigue (65.7%), dermatitis acneiform (60.0%), diarrhoea (54.3%), nausea (48.6%), and oedema peripheral (48.6%). CTCAE Grade ≥3 AEs were reported in 58.9% of patients including 71.4% in the AZD6244 75 mg bd combined cohort. With the exception of 1 CTCAE Grade 4 AE (hypoglycaemia), the majority of event terms were reported by only 1 patient at CTCAE Grade 3.

Small increases in blood pressure were observed within the first week of continuous treatment with AZD6244; maximal median increases were apparent at after 3 weeks treatment with AZD6244 75 mg bd (systolic +7 mmHg; diastolic +13 mmHg) with improvement within 4 weeks of continuing treatment (to median +1 mmHg and +2 mmHg).

The scheduled 8 week assessments of left ventricular ejection fraction (LVEF) was carried out to evaluate a possible cardiac aetiology of the peripheral oedema reported in earlier studies. A median reduction from baseline of 6.5 percentage points (range -25 to +10 percentage points) was recorded in patients receiving AZD6244 75 mg bd. AEs of left ventricular dysfunction or ejection fraction decreased have been reported in 8.6% of patients receiving AZD6244 75 mg bd in Study D1532C00005.

There were no clinically significant changes in pulse rate, blood oxygen saturation, ECG parameters (including QTc) or haematology assessments, and no new clinically significant effects on laboratory parameters were observed.

One patient (with *BRAF* mutation positive cutaneous melanoma) had a complete response during treatment with AZD6244 75 mg bd in Study D1532C00005 for >5 years (Boers-Sonderen et al 2012). In addition, 16 (45.7%) patients had stable disease of ≥6 weeks, and 10 (18.2%) patients had stable disease of ≥16 weeks (Banerji et al 2010).

The final safety data from patients who received AZD6244 100 mg bd in the 4 completed Phase II monotherapy studies of AZD6244 free base suspension (D1532C00003, D1532C00008, D1532C00011 and D1532C00012) are summarised below.

The most frequently reported all causality AEs in the pooled population of patients receiving AZD6244 100 mg bd free base suspension in Phase II monotherapy studies are presented.

Rashes (including the preferred terms dermatitis acneiform, rash, rash maculopapular, rash macular, rash papular, acne and folliculitis), were reported in approximately 70% of patients receiving treatment with AZD6244, and dermatitis acneiform was the most common AE term overall (53.9%). Other commonly reported AEs were diarrhoea (49.4%), nausea (32.7%) and vomiting (23.8%). AEs of peripheral oedema, periorbital oedema or facial oedema were reported in 30.9%, 8.6% and 4.1% of patients, respectively. AEs of fatigue or asthenia were reported in approximately 30% of patients in this Phase II population. Dyspnoea exertional or dyspnoea was reported in 13% of patients and, in individual studies, dyspnoea exertional was reported at a higher incidence in the AZD6244 groups than in the comparator chemotherapy groups.

SAEs were reported in 23.8% of patients receiving AZD6244 monotherapy. The most frequently reported SAEs were vomiting (1.5%), diarrhoea, erysipelas and pulmonary embolism (in 1.1% patients each). SAEs of infections (bacterial sepsis, sepsis, infection, bacterial arthritis) were reported in 2.2% of patients.

Small increases in systolic and diastolic blood pressure have been reported in patients receiving AZD6244. In Study D1532C00003, small increases in blood pressure were observed after 1 week on AZD6244, with mean increases of 7.4 mmHg (systolic blood pressure) and 5.3 mmHg (diastolic blood pressure) at Week 8, compared with mean increase of 1.1 mmHg (systolic blood pressure) and 0.5 mmHg (diastolic blood pressure) in the temozolomide comparator arm. AEs of hypertension were reported in 18 patients (6.7%) receiving AZD6244 in Phase II monotherapy studies; 6 of these patients had hypertension at entry to the study, and a further 5 patients had documented risk factors for hypertension (diabetes, hypercholesterolaemia, smoking status).

Scheduled on-treatment assessments (Week 4) of left ventricular ejection fraction (LVEF) were included in one Phase II study (D1532C00003) to evaluate a possible cardiac aetiology of the peripheral oedema reported in earlier studies. The median change in LVEF at Week 4 was -1.2 percentage points, and the individual change from baseline ranged from –20 to +19 percentage points. No comparative data are available from the temozolomide group as Week 4 assessments were not mandated for these patients. AEs of ejection fraction decreased, left ventricular dysfunction, or ventricular dysfunction were reported in a total of 6 patients (2.2%) receiving AZD6244 in Phase II monotherapy studies, and all AEs occurred in the study that included scheduled on-treatment assessments of LVEF (including 3 patients who had switched from temozolomide treatment after disease progression):

- In 2 patients, the change from baseline was less than 10 percentage points and LVEF remained above 55%.

- Reversible decreases in LVEF of ≥10 percentage points and to below 55% occurred in 2 patients.
  - Reduction of 9 percentage points to 46%, which subsequently recovered to 64% after discontinuation of AZD6244.
  - Asymptomatic reduction from 53% at baseline to 39%, reversible to 52% on stopping AZD6244 (SAE).
- Gradual onset of reversible left ventricular diastolic dysfunction (LVEF 60%) in a patient with extensive concomitant cardiac disease (SAE).
- LVEF value was not recorded for the remaining patient with an AE report of reversible left ventricular dysfunction.

No clinically significant trends in ECG parameters, including QTc, were observed in patients receiving AZD6244 monotherapy.

Laboratory parameters

Review of clinical laboratory parameters in Phase II monotherapy studies identified a trend towards increased ALT and AST levels after starting treatment with AZD6244. An increase in serum phosphate was observed in some patients after initiation of AZD6244, compared with patients randomised to comparator treatments.

There was a trend towards a small mean decrease in albumin compared with comparator. No other reports of AZD6244 related changes in laboratory parameters are considered to be of clinical relevance at this time. There was no evidence of myelosuppression or renal impairment.

This section lists those events that are to be regarded as expected for regulatory reporting purposes as documented in Section 5.4 of the Investigator Brochure.

- Gastrointestinal: diarrhoea, nausea, vomiting, stomatitis (oral mucositis), dry mouth.
- Skin and subcutaneous: rashes (including dermatitis acneiform and exfoliative rash), dry skin, paronychia.
- General: facial and/or peripheral oedema, fatigue/asthenia, pyrexia.
- Respiratory: dyspnoea.
- Eye: blurred vision.
- Physical assessments: increased blood pressure, reduced left ventricular ejection fraction.

- Laboratory changes: increases in serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT), hypoalbuminemia, hyperphosphataemia, which may be associated with an increase in calcium x phosphate product requiring therapeutic intervention.

9. STUDY DESIGN AND RATIONALE

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

9.1 Overall study design and flow chart

This part of the Phase I, open-label study aims to investigate the safety, tolerability and pharmacokinetic profile of oral doses of AZD6244 when administered as a monotherapy in Japanese patients with advanced solid malignancies.

Approximately 12 Japanese patients with advanced solid malignancies refractory to standard treatment or for which no standard therapy exists will be recruited from 2-3 sites in Japan.

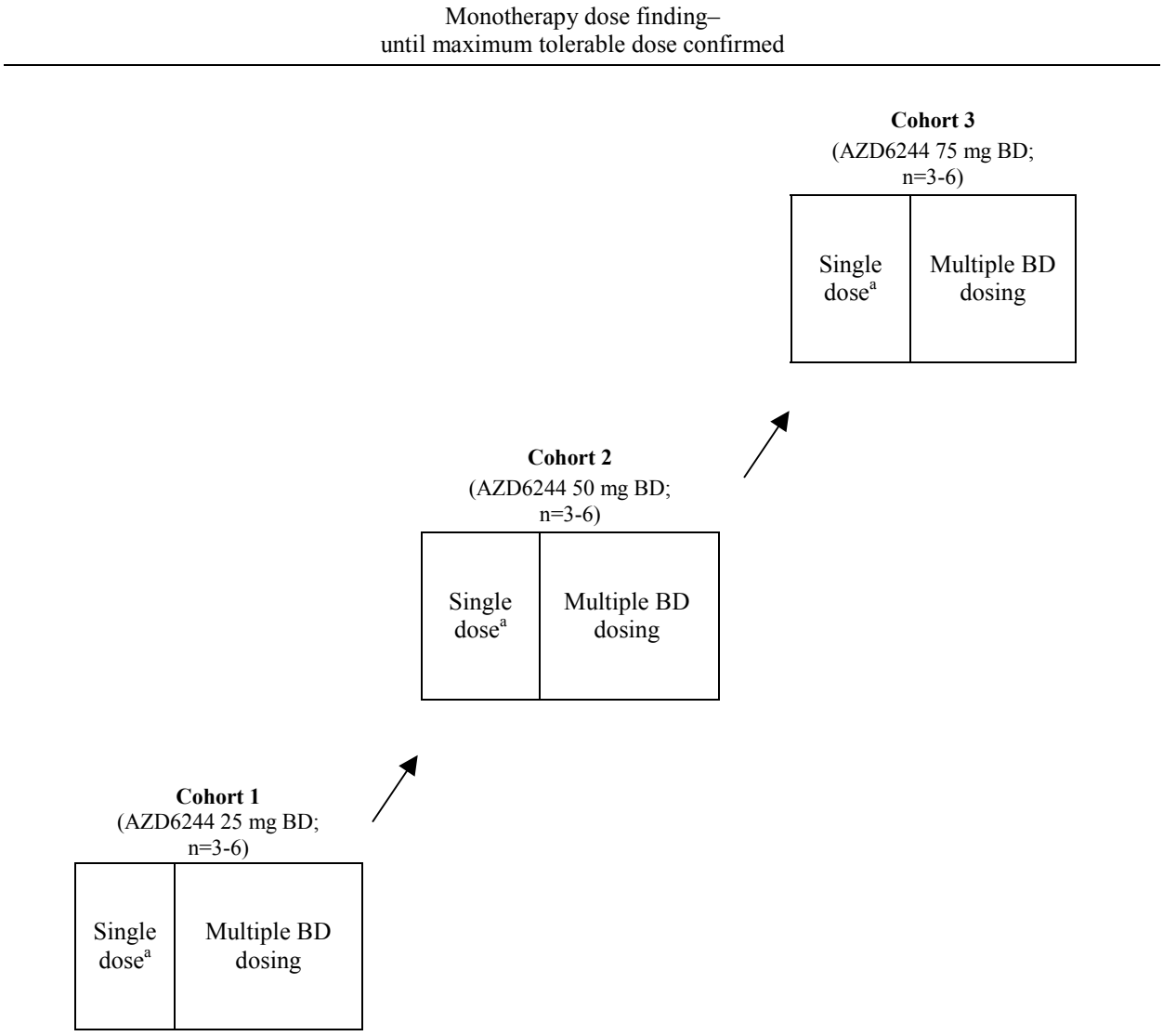
The starting dose of monotherapy part will be AZD6244 25 mg (1 x 25 mg capsule). One single oral dose of AZD6244 (25 mg) will be administered on the morning of Day 1, followed by a washout of a minimum of 3 days, and then multiple oral dosing twice daily (25 mg dose in both the morning and evening). At least 3 evaluable patients will be enrolled in Cohort 1. If this cohort is identified as tolerated by SRC, then it will be escalated to the next cohorts (Cohort 2 and 3).

The single dose period will be defined as Cycle 0, which starts at a single dose on Day 1 until the day before the first dose of multiple dosing. Cycle 1 will be a 21-day dosing period.

The DLT assessment period consists from the first dose of AZD6244 to before the Cycle 2. After Cycle 1, patients may continue on Cycle 2, 3, and 4 and onwards of multiple daily dosing. Each Cycle is defined as a 21-day dosing period.

Patients continuing to tolerate the treatment and receiving any clinical benefit from the treatment may repeat this schedule, until no clinical benefit is apparent (ie, patient has progressive disease), or the patient is withdrawn for other reasons, provided that another written consent on continuous treatment should be obtained from patients before the start of Cycle 2. Investigators may decide to suspend or decrease the dose of AZD6244 if significant toxicity develops.

Figure 2 Flow chart: Monotherapy part



a Washout period will be a minimum 3 days.

9.2 Rationale for conducting this study and for study design

This study has been started as a Phase I open-label study to investigate the safety, tolerability and pharmacokinetic profile of oral doses of AZD 6244 when given in combination with docetaxel in Japanese patients with NSCLC. Total eight eligible patients have been enrolled to the combination therapy cohort of this study. As DLTs of febrile neutropenia of CTCAE Grade 4 were reported in 2 of 4 patients randomised to Cohort 1 (given AZD6244 75 mg BD and docetaxel 60 mg/m^2 every 21 days), SRC assessed that the dose of this Cohort was a non-tolerable dose. After that, a DLT of febrile neutropenia of CTCAE Grade 4 was reported in one of 4 patients randomised to Cohort 2 (given AZD6244 25 mg BD and docetaxel 60 mg/m^2

every 21 days). Thus, the investigation of the concomitant therapy with docetaxel was suspended, and it was determined to investigate the tolerability and pharmacokinetic profile in patients given AZD6244 monotherapy.

Limited efficacy data have been available from 3 Phase I studies of AZD6244 in patients with advanced solid tumors which had objective tumour response as an exploratory endpoint.

In Study ARRY-0401 the best overall response of stable disease was recorded in 27.9% of patients receiving AZD6244 100 mg bd. Long term (≥5 months) stable disease was observed in 9/57 patients, 6 of whom had melanoma (Adjei et al 2008).

One patient (with *BRAF* mutation-positive cutaneous melanoma) had a complete response during treatment with AZD6244 75 mg bd in Study D1532C00005 for >5 years (Boers-Sonderen et al 2012). In addition, 16 (45.7%) patients had stable disease of ≥6 weeks, and 10 (18.2%) patients had stable disease of ≥16 weeks (Banerji et al 2010).

In Study D1532C00020, 2 (7.1%) patients had partial responses; both patients had malignant melanoma, and were noted to still be alive and continuing study treatment at data cut-off. In addition, 5 (17.9%) patients had stable disease for >100 days.

The starting dose in the monotherapy part of this study is AZD6244 25 mg BD, the lowest dose used in the combination therapy part of this study. If this dose is well tolerated, the dose of AZD6244 50 mg BD will be investigated in the next cohort. The dose for the investigation is scheduled to be increased up to 75 mg BD which is the MTD determined in the non-Asian Phase I study to invesetigate monotherapy (D1532C00005).

10. PATIENT SELECTION AND RESTRICTIONS

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

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

10.1 Inclusion criteria

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

1. Provision of written informed consent.

2. Patients must be ≥ 20 years.

3. Patients with advanced solid malignancies refractory to standard treatment or for which no standard therapy exists irrespective of the stage and previous treatment.

4. Patients with histologically or cytologically confirmed advanced solid malignancies.

5. World Health Organisation (WHO) performance status 0-1.

6. Evidence of post-menopausal status or negative urine/serum pregnancy test for non-menopausal female patients.

   Women will be considered postmenopausal if they are amenorrheic for 1 year or more without an alternative medical cause. The following age-specific requirements apply:

   i) Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 1 year or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range.

   ii) Women over 50 years of age would be consider postmenopausal if they have been amenorrheic for 1 year 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).

7. Patients must have calculated creatinine clearance > 50 mL/min using Cockcroft-Gault formula (see Appendix M) or by 24 hour urine collection.

8. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT or MRI and is suitable for repeated assessment.

9. Patients must be able to swallow AZD6244 capsules.

10. Patients must have a life expectancy ≥ 16 weeks.

11. Evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on Cycle 0 Day 1 and every 9 weekly relative to date of Cycle 4 Day 1.

12. Patient is willing to provide a fresh, or archival tumour biopsy.

13. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.

14. Patients can remain in Hospital from Cycle 0/Day 1 (Visit 2) up to at least the completion of Cycle 2/Day 1 (Visit 9).

For inclusion in the optional biomarker research or pharmacogenetic component of the study, patients must provide specific informed consent. If a patient declines to participate in the

optional biomarker research or pharmacogenetic component of the study, there will be no penalty to the patient. The patient will not be excluded from the therapeutic study described in this Clinical Study Protocol.

10.2 Exclusion criteria

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

1. Prior treatment with a MEK inhibitor.

2. Previous enrollment or assignment to treatment in the present study.

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

4. Participation in a clinical study during the last 30 days or have not recovered from side effects of an investigational study drug.

5. Recent major surgery within 4 weeks prior to consent (excluding the placement of vascular access).

6. Radiotherapy or standard chemotherapy within 21 days prior to entry into the study (not including palliative radiotherapy at focal sites).

7. Brain metastases or spinal cord compression unless treated and stable (for at least 1 month) off steroids.

8. Evidence of active infection or active bleeding diatheses.

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

10. Patients with factors that increase the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome) or QTc interval of > 450 ms for males or > 470 ms for females on screening.

11. Evidence of severe or uncontrolled systemic disease (eg, severe hepatic impairment, severe renal impairment, uncontrolled diabetes, acute uncontrolled infection) or current unstable or uncompensated respiratory or cardiac conditions and baseline LVEF ≤ 55% or peripheral vascular disease including diabetic vasculopathy, or renal transplant.

12. Patients with documented cases of human immunodeficiency virus (HIV) or active hepatitis B or C infection.

13. Laboratory values as listed below:

- Absolute Neutrophil Count (ANC) < 1500 per mm^3
- Platelets < 100000 per mm^3
- Hemoglobin (Hb) < 9.0 g/dL
- Serum bilirubin ≥ 1.5 x Upper Limit of Normal (ULN) (known Gilbert's disease excluded)
- Aspartate aminotransferase (AST/SGOT) or alanine aminotransferase (ALT/SGPT) ≥ 2.5 x ULN or 5 x ULN if liver metastases
- Patients with proteinuria > 2 g/24 hr urine collection are excluded

14. Clinical judgment by the Investigator that the patient should not participate in the study.

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

16. Use of strong CYP1A2 or 3A4 inducers and/or inhibitors (for example, but not limited to, ketoconazole, rifampicin, atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit or grapefruit juice, rifabutin, phenytoin, carbamazepine, phenobarbital and St. John's Wort).

10.3 Restrictions

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

1. Reliable methods of contraception should be used consistently and correctly. Some examples of acceptable contraceptive methods are shown below.

   <Barrier method>

   - condom plus spermicide (tablet or jelly, etc.)

   <Other contraceptive methods>

   All the following methods should be used together with a barrier method (condom or spermicide).

   - oral contraceptives
   - intra-uterine device

- vasectomy of partner

Preliminary reproductive toxicology data indicate that AZD6244 can have adverse effects on embryo fetal development and survival at dose levels that do not induce maternal toxicity in mice.

Therefore, patients who are pregnant or actively breast feeding are not eligible to participate in this study. Also female patients of child bearing potential will be required to use reliable methods of contraception for the duration of the study and until 4 weeks after the last dose of study treatment. Male patients will be required to use reliable methods of contraception for the duration of the study and until 3 months after the last dose of AZD6244 treatment.

Thus both male and female subjects should use acceptable contraceptive methods during the study and for 3 months after the last dose of AZD6244.

2. The maximum dose of vitamin E patients may receive from AZD6244 is approximately 210 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided in patients receiving the capsule formulation.

3. Patients who are taking coumadin anticoagulants (eg, warfarin) should have their anticoagulation tested more frequently while taking AZD6244.

4. Throughout the study, patients should avoid changes to or the addition of all concomitant medications, in particular any that are likely to affect the metabolism of AZD6244 (see Section 10.2 Exclusion criteria No.16), unless considered clinically essential for management of concurrent conditions.

5. Grapefruit juice and Seville orange or the juices of these fruits must not be consumed while participating in the study.

6. Patients should avoid excessive sun exposure and use adequate sunscreen protection (SPF45 or higher or PA+++ or higher) if sun exposure is anticipated.

7. No food or drink other than water for 2 hours prior to dosing and 1 hour after dosing.

For restrictions relating to concomitant medications see next Section 10.3.1.

10.3.1 Concomitant treatments

- Blood transfusions are allowed at any time during the study, if clinically indicated to treat anaemia. Blood transfusions should not be used prophylactically during Cycle 1.

- Throughout the study, patients should avoid changes to, or the addition of all concomitant medications, in particular any that may affect the metabolism of

AZD6244 (see Section 10.2 Exclusion criteria No.16), unless considered clinically indicated.

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

- Patients may take warfarin or a coumarin preparation but it is recommended that they should have their anticoagulation monitored carefully and dose adjusted accordingly.

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

- No other standard cancer agents, or investigational drugs should be administered while patients are receiving study medication. Supportive treatments including hormonal and bisphosphonate therapies are allowed.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the CRF. Trade name, generic name, indication, route of administration, dates of administration etc, should be properly documented.

11. STUDY TREATMENT AND CONDUCT

11.1 Treatment

AZD6244 drug product will be provided by AstraZeneca Pharmaceutical Development Supply Chain.

The AZD6244 capsule contains AZD6244 Hydrogen Sulfate equivalent to 25 mg of AZD6244 free base. Capsules are packaged in high-density polyethylene (HDPE) bottles. Additional information about the investigational product may be found in the Investigators' Brochure.

Dosing should not occur until pre-dose blood samples and other study procedures have been completed. AZD6244 will be administered orally in the morning in Cycle 0/ Day 1 and in the morning and evening (twice daily) in Cycle 1/ Day 1 and after. The dose interval should be preferably approximately 12 hours apart and in the fasting condition. The patient should refrain from eating for at least 2 hours pre-dose and 1 hour post-dose (only water will be permitted). In the case of vomiting after taking a tablet and incompliance re-dosing should not be performed.

In the study, following at least 1 cycle, patients may continue to receive AZD6244 until disease progression occurs or as long as they do not experience intolerable toxicity and the investigator believes they are continuing to derive benefit from the therapy.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text will be written by Japanese IPS.

All study drugs should be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified in the document 'Handling Instruction of Investigational Product'.

11.1.1 Starting dose, dose escalation scheme and stopping criteria

11.1.1.1 Monotherapy regimen dose finding

Patients with confirmed eligibility will be enrolled according to the standard clinical management of their disease.

Dosing will begin at one single oral dose of AZD6244 (25 mg), which will be administered on the morning of Day 1, followed by a washout of minimum 3 days, and then multiple oral dosing twice daily AZD6244 25 mg BD (each in the morning and evening) will begin (Cohort 1). The single dose period will be defined as Cycle 0, which starts at a single dose on Day 1 until the day before the first dose of multiple dosing. Cycle 1 will be a 21-day period from the first dose of multiple dosing.

1. A minimum of 3 evaluable patients will be enrolled for Cohort 1:

If 0/3 evaluable patients experience a DLT within first cycle of commencing treatment then patients will be enrolled at the next dose level, 50 mg twice daily (Cohort 2).

If 1/3 evaluable patients experience a DLT within first cycle of commencing treatment a further 3 patients will be recruited at this dose level (to treat a maximum of 6 patients before further escalation is considered).

Then if;

1/6 evaluable patients experience a DLT, then the dose will be escalated to the next dose level, 50 mg twice daily (Cohort 2).

At any stage if ≥ 2 evaluable patients experience a DLT, recruitment to the cohort will cease and that monotherapy regimen dose will be defined as a non-tolerated dose, and a step to proceed to recruitment to the next Cohort.

2. If monotherapy regimen dose is escalated to the next cohort (Cohort 3), a minimum of 3 evaluable patients will be enrolled for Cohort 3, 75 mg twice daily multiple dose.

If 0/3 or 1/3 evaluable patients experience a DLT within first cycle of commencing treatment then a total of 6 patients will be enrolled in this cohort to confirm the safety and tolerability.

At any stage if ≥ 2 evaluable patients experience a DLT, recruitment to the cohort will cease and that monotherapy regimen dose will be defined as a non-tolerated dose.

Monotherapy regimen dose escalation/decrease decisions will be made jointly, between investigators and AstraZeneca, meeting as a SRC prior to the opening of each cohort. Decisions will follow medical review of available clinical and laboratory data.

There will be no intra-patient dose escalation of AZD6244 this study. If patient experiences an AZD6244 related toxicity, their individual dose may be reduced or withheld at the investigators discretion. All cohort monotherapy regimen dose escalation/reductions will occur in consultation with the SRC. Once a patient has received an AZD6244 dose reduction, there is no provision for re-escalation or re-challenge with a higher dose.

11.1.2 Definition of dose-limiting toxicity

Dose-limiting toxicity (DLT) is defined as any of the following occurrences during the first cycle of single dose until before Day 1/Cycle 2 when considered related to AZD6244 treatment.

Hematologic Toxicities:

- Afebrile Grade 4 neutropenia > 5 days or Grade 4 neutropenia associated with fever (reading of body temperature > 38.5°C or 3 readings of body temperature > 38.0°C in a 24-hour period).

- Grade 4 thrombocytopenia

Non-Hematologic Toxicities:

- > Grade 3 non-hematological toxicities for > 7 days should be considered a potential DLT that will be finally assessed whether to be definitely DLT or not at the Safety Review Committee. Grade 3 non-hematological toxicities that can be controlled to Grade 2 or less within 7 days with appropriate interruption of treatment with AZD6244 (Section 11.1.5.1) and treatment will not be considered dose limiting. Grade 3 events that do not resolve to CTC grade ≤ 2 events within 7 days despite appropriate treatment interruption and optimal supportive therapy will be considered dose limiting.

If a drug-related DLT should occur after Cycle 1, the course of action to be taken will be decided by consensus of the principal investigators and the sponsor.

For dose escalation purposes, only DLT occurring from Day 1 Cycle 0 until the the last day of Cycle 1 will be considered. SRC will make decisions regarding monotherapy regimen dose escalation steps.

Monotherapy regimen dose escalation will stop if the defined number of patients in any cohort experiences DLT.

11.1.3 Definition of evaluable patient

For dose escalation decisions, an evaluable patient is defined in principle as a patient who need to have (1) completed at least 75% of planned daily doses of AZD6244 in the first 21 days of multiple dosing period and has enough information to be assessed for the dose escalation (If a patient has less than 75% compliance, the patient will not be considered evaluable but will be included in the safety assessment), or (2) experienced a DLT during the first cycle of single dose until before Day 1/Cycle 2.

Patients withdrawing from treatment for reasons other than (1) or (2) above before completing the evaluation period (up to the period before Cycle 2 Day 1) will be replaced.

11.1.4 Safety Review Committee

After completion of Cohort 1, a SRC will evaluate the safety and tolerability of AZD6244 to determine the dose levels in the next cohort.

The SRC will consist of:

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

In addition, one other physician from the following may be invited:

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

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

Further internal or external experts may be consulted by the SRC as necessary. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

Once there are at least 3 evaluable patients at a dose level the SRC will review and assess all available safety data from the cohort to make a decision on the dose for the next cohort of patients. Any dose interruptions and reductions will be taken into account.

The decision may be to (refer to Section 11.1.1)

1. Expand the cohort
2. De-escalate and investigate a lower dose of AZD6244 in the next cohort

3. Escalate to investigate a higher dose of AZD6244 in the next cohort

4. Stop the study

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

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

11.1.5 Management of study treatment related toxicity

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.

11.1.5.1 AZD6244 related toxicity

Adverse events considered related to administration of AZD6244 are listed in Section 5.4 of the Investigator Brochure. If any adverse events of dyspnoea, asymptomatic decreases in LVEF or diarrhoea occur that are considered at least partly due to administration of AZD6244, algorithms for the investigation and management of these events are provided in Appendices J, K and O respectively. For all adverse events reported in this study that are considered at least partly due to administration of AZD6244 the following dose reduction/adjustment guidance should be applied:

Treatment with AZD6244 should be withheld if one of the following toxicities considered related are observed, despite optimal supportive care:

- Any intolerable adverse event regardless of grade
- Any adverse events ≥ CTCAE Grade 3

AZD6244 treatment may not be restarted until the toxicity improves to CTCAE Grade 1 or baseline, except for rash where patients with CTCAE Grade 2 rash may restart treatment. Additional information on the management of skin toxicity is provided in Section 11.1.5.2 of this protocol.

Treatment may be resumed at the original dose or at a permanently reduced dose at the discretion of the investigator.

If a patient experiences an occurrence of a new toxicity requiring treatment interruption once having restarted on treatment, study medication should again be withheld until the toxicity improves to CTCAE Grade 1 or baseline except for rash where CTCAE Grade 2 rash is acceptable. Upon recovery, treatment may resume at the previous dose level or the dose can be reduced.

However, if a patient experiences recurrence of the same toxicity as that causing a previous dose interruption and/or dose reduction, study medication should be withheld until the toxicity improves to CTCAE Grade 1 or baseline, except for rash where CTCAE Grade 2 rash is acceptable. Upon recovery, treatment should resume at a permanently reduced or adjusted dose.

Dose reduction/adjustment

25 mg twice daily:

If a patient experiences a novel toxicity that cannot be adequately managed by dose interruption and medical interventions then the patient must discontinue AZD6244 treatment, as no further dose reductions/adjustments are permitted.

50 mg twice daily:

- 50 mg once daily, if no dose reduction has yet occurred
- 25 mg twice daily: dose adjustment if dose reduction to 50 mg once daily has already occurred

75 mg twice daily:

- 75 mg once daily, if no dose reduction has yet occurred
- 50 mg twice daily: dose adjustment if dose reduction to 75 mg once daily has already occurred
- 50 mg once daily: dose adjustment if dose reduction to 75 mg once daily followed by dose adjustment to 50 mg twice daily has already occurred
- 25 mg twice daily: dose adjustment if dose reduction to 75 mg once daily and 50 mg twice daily followed by dose adjustment to 50 mg once daily has already occurred

Once reduced/adjusted, the dose cannot be returned to the previous level.

If a patient experiences recurrence of any toxicity that has already contributed to dose reductions down to the lowest dosing schedule for this study (25 mg twice daily), the patient must discontinue AZD6244 treatment.

If a patient receiving the lowest dosing schedule (25 mg twice daily) experiences a novel toxicity that cannot be adequately managed by dose interruption and medical interventions then the patient must discontinue AZD6244 treatment, as no further dose reductions/adjustments are permitted.

All dose delays, reductions and adjustments will be recorded in the appropriate electronic Case Report Form (eCRF).

Dose re-escalation of AZD6244 is not permitted in this study.

In the event of any dose delay/reduction/adjustment, patients should continue to follow the assessments schedule as described in Table 4 study plan relative to baseline.

11.1.5.2 Algorithm for Management of Skin Toxicity

The aetiology of skin toxicities associated with the use of AZD6244 is uncertain. An algorithm based on dermatology best practices for other contemporary targeted agents that cause skin toxicity (Pérez-Soler et al 2005) is offered as guidance for managing skin toxicities seen in patients being treated on this protocol.

The algorithm suggests a step-wise approach to rash management. If the rash is CTCAE Grade 1, consider starting with topical steroids, topical antibiotics such as clindamycin gel, or no treatment if the patient is asymptomatic. A high potency topical steroid cream, such as clobetasol propionate, may be considered early in patients with mild rash and may be used on the face.

If the rash is CTCAE Grade 2, consider adding an oral tetracycline and/or pimecrolimus cream or similar agent.

If the rash reaches CTCAE Grade 3 or above, dose interruption and/or dose reduction/ adjustment, coupled with the addition of topical steroids is recommended.

Pruritus of any grade may be treated with an antihistamine, such as diphenhydramine or hydroxyzine hydrochloride.

Secondary infection may complicate or worsen skin toxicity. To reduce the likelihood of nasal infection, intranasal mupirocin may be considered. Infected rash may be treated with a short course of an oral tetracycline, such as minocycline hydrochloride. If there is a clinical diagnosis of impetigo, or an infection with Staphylococcus aureus is confirmed, topical mupirocin might be used. Infected lesions suspected to be treatment resistant should be cultured. If there is no improvement after two weeks of treatment, therapy for the rash should be considered ineffective and discontinued. All required treatment information and adverse event information for rash should be recorded on the appropriate CRF.

11.1.6 Duration of therapy

Patients must remain in Hospital from Cycle 0/Day 1 (Visit 2) up to the completion of Cycle 2/Day 1 (Visit 9).

Patients may continue to receive AZD6244 as long as they are continuing to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria (see Section 11.4).

11.1.7 Treatment compliance and accountability

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca.

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

The unused drugs and empty containers are returned to the AZKK and not destroyed. And the details are shown in 'Handling instruction of Investigational Product' that AZKK provides to sites.

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

11.1.8 Doses and treatment regimens

11.1.8.1 AZD6244 capsule formulation

AZD6244 capsule formulation drug product is supplied as 25 mg capsules in high-density polyethylene (HDPE) bottles.

If patients are not able to tolerate AZD6244, dose reductions are permitted as described in Section 11.1.5.1. Reduced doses will depend on available capsule strengths and the required total daily dose.

Patients will be instructed as to when and how many capsules to use each day.

Study sites will ensure that patients are compliant with treatment.

11.1.8.2 AZD6244 Dosing

Throughout the study no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing. Dosing on a PK day should not occur until pre-dose blood samples and other study procedures have been completed.

The doses should be taken approximately 12 hours apart for example 08:00h and 20:00h or 09:00h and 21:00h.

11.2 Rationale for dose regimen, dose finding scheme and stopping criteria

This study is a Phase I, open-label, dose-finding study. The monotherapy part of this study is designed to investigate the safety, tolerability and pharmacokinetic profile of oral doses of AZD6244 when given as a monotherapy in Japanese patients with advanced solid malignancies.

The starting dose of AZD6244 in the monotherapy part of this study is AZD6244 25 mg BD. If this is well tolerated then the dose of AZD6244 will be increased to 50 mg BD, then

increased to the highest dose up to 75 mg BD which was the MTD of AZD6244 in Phase I monotherapy study in non-Asian patients (D1532C00005). If this dose is not well tolerated, AZD6244 may be investigated with the lower dose in the next cohort.

Cohorts of 3 to 6 patients will be recruited during the dose finding phase to allow for early discontinuations and the observation of a minimum of 3 evaluable patients per cohort.

This approach is justified by the fact that the monotherapy regimen dose escalation will commence in the region of pharmacological activity based on the clinical information to date.

The information from this study will be used to determine the safety, tolerability and PK profile of doses of AZD6244 when administered as monotherapy in Japanese patients, and could guide selection of future doses to be used in combination regimens.

11.3 Benefit/risk and ethical assessment

Limited efficacy data are available from 3 Phase I studies of AZD6244 in patients with advanced solid cancer which had objective tumour response as an exploratory endpoint.

In Study ARRY-0401 the best overall response of stable disease was recorded in 27.9% of patients receiving AZD6244 100 mg bd. Long term (≥5 months) stable disease was observed in 9/57 patients, 6 of whom had melanoma (Adjei et al 2008).

One patient (with *BRAF* mutation-positive cutaneous melanoma) had a complete response during treatment with AZD6244 75 mg bd in Study D1532C00005 for >5 years (Boers-Sonderen et al 2012). In addition, 16 (45.7%) patients had stable disease of ≥6 weeks, and 10 (18.2%) patients had stable disease of ≥16 weeks (Banerji et al 2010).

In Study D1532C00020, 2 (7.1%) patients had partial responses; both patients had malignant melanoma, and were noted to still be alive and continuing study treatment at data cut-off. In addition, 5 (17.9%) patients had stable disease for >100 days.

The monotherapy part of this study D1532C00067 is therefore designed to confirm toxicity profile of AZD6244, and to investigate the safety, tolerability and pharmacokinetic profile of AZD6244 oral administration monotherapy in Japanese patients with advanced solid malignancies of AZD6244 as well as the apropriateness of the dose escalation to further proceed the ongoing combination therapy part with docetaxel.

The starting dose of AZD6244 is 25 mg BD which is the lowest dose investigated in the ongoing combination therapy part. If this is well tolerated then the dose of AZD6244 50 mg BD will be investigated in the next cohort. The highest dose to be investigated will be 75 mg BD which was the MTD of AZD6244 Phase I monotherapy study in non-Asian patients (D1532C00005).

In case of any intolerable and severe AEs, the Investigator should follow the instructions provided in Section 11.1.5 and mitigate the risk to a patient by applying suggested dose reduction/adjustment algorithms for AZD6244.

AstraZeneca believes that the investigation of AZD6244 monotherapy in patients with advanced solid malignancies is justified, based on the emerging safety profile from Phase I monotherapy studies; ARRY-0401, D1532C00005 and D1532C00020.

As a part of this study the patients will undergo standard clinical evaluations, including physical exams, registration of vital signs and basic biometric parameters, safety laboratory evaluations (haematology, chemistry, urinalysis), regular pregnancy tests (where applicable), ECGs, CT/MRI and echocardiogram/MUGA. Diagnostic procedures and assessments mandated by the study protocol were designed with the consideration of safety profiles of AZD6244. The types and frequency of assessments are aligned to the current healthcare standards with additional precaution and increase in examinations during the first two 3-weekly cycles of treatment (Cycle 0 and Cycle 1) to ensure timely detection of any early treatment emergent safety signals.

Adverse events related to visual function have been reported at a low frequency in most monotherapy studies with AZD6244. There were no specific clinical findings reported from patients that underwent ophthalmological evaluation after reporting the AE of visual disturbance. To further assess and document any clinical effects that may be linked to development of visual function adverse events in patients receiving AZD6244, a full ophthalmological examination should be conducted at baseline, at Cycle 3 and on the occurrence of any visual disturbance adverse event.

Some patients receiving AZD6244 have been observed to develop asymptomatic decreases in LVEF in the absence of confounding comorbidities. AstraZeneca continues evaluation of LVEF changes in patients receiving AZD6244 and collects baseline and sequential measurements of LVEF and end systolic and diastolic ventricular volumes on echocardiogram/MUGA. As a part of this study, the levels of Troponin I will also be monitored to see if they can help detect any early signs of deterioration of cardiac function.

Given the extensive safety monitoring included in this study, and inclusion of a full review of available safety, tolerability and pharmacokinetic data prior to each monotherapy regimen dose escalation decision, AstraZeneca believes that the overall risk for the patients who participate in this study would be acceptable.

11.4 Discontinuation of investigational product and withdrawal from study

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

- Patient decision. The patient is at any time free to withdraw his/her participation in the study, without prejudice
- Safety reasons as judged by the investigator and/or AstraZeneca
- Adverse events

- Severe non-compliance to this protocol as judged by the investigator and/or AstraZeneca
- Confirmed disease progression
- Patients incorrectly initated on investigational product (Section 11.4.1)
- Patient becomes pregnant
- Patient lost to follow-up

Any patient who permanently discontinues investigational product will be withdrawn from the study (Section 11.4.2).

Patients that are withdrawn from the study but are evaluable per the definition in Section 11.1.3 will not be replaced. Any patient that is withdrawn and is not evaluable will be replaced to ensure a minimum number of evaluable patients.

Patients may withdraw from any aspects of the voluntary exploratory research (see Section 16) at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Section 17.5.

11.4.1 Procedures for handling patients incorrectly initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be initiated on investigational product. There can be no exceptions to this rule.

Where patients start the study treatment in error eg, where patients are subsequently identified as having failed to meet the inclusion/exclusion criteria, the procedures included in the protocol for the discontinuation of such patients must be followed (see Section 11.4.2).

11.4.2 Procedures for withdrawal from study

A patient that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The Principal Investigator/Sub-Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. They will also immediately inform AstraZeneca of the withdrawal. Adverse events should be followed up (see Sections 13.3 and 13.4) and study drug should be returned by the patient.

11.5 Study timetable and end of study

The end of this study is defined as the date of the last visit of the last patient, occurring when all patients have completed study therapy.

Planned duration of the study:

Study period: April, 2012 - June, 2014

Registration period: April, 2012 – January, 2014

There will be a data cut-off defined as the earlier of 6 months after the last patient recruited starts investigational product or follow up visit at 28 days after the final patient discontinues investigational product. Data analysis will be performed and a Clinical Study Report written based on this data set.

Any patients still continuing on the study at the time of this data cut-off will be able to continue to receive AZD6244 while deriving clinical benefit. Such patients will continue to be monitored up to 28 days after the last dose of investigational product. A Clinical Study Report Addendum will be prepared to summarise the additional safety data collected between the data cut-off and the end of the study.

12. STUDY PLAN AND COLLECTION OF STUDY VARIABLES

12.1 Study Plan

Table 4 Study plan (Monotherapy Part)

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14+** [a]	Discontinuation from treatment	
Visit Description	Screening	Treatment Period													Treatment Discontinuation Visit	28 days post last dose of last study treatment
Cycle		0				1			2			3	4	5		
Day	-14 to –1	1	2	3	4	1	8	15	1	8	15	1	1	1	N/A	N/A
Visit Window (compared to Day 1)	N/A	N/A				* [b]	±2 days	±2 days	±2 days	±2 days	±2 days	±1 wk	±1 wk	±1 wk	N/A	±7 days (compared to trt disc visit)
Main study informed consent	X								X[c]							
Demography (date of birth, sex, race)	X															
Patient background (histology, disease staging, medical and surgical history, concomitant disease, previous cancer therapy, smoking status)	X															
Archival tumour sample- original archival diagnostic or more recent (pre-study) archival biopsy [d]	X															
Optional at progression fresh biopsy [d]															(X)	
Optional blood sample for genetic research [f]		(X)														
Optional blood sample for biomarker analysis [g]	(X)					(X)	(X)		(X)			(X)		(X)	(X)	
Adverse events [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [h]
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4 Study plan (Monotherapy Part)

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14+** [a]	Discontinuation from treatment	
Visit Description	Screening	Treatment Period													Treatment Discontinuation Visit	28 days post last dose of last study treatment
Cycle		0				1			2			3	4	5		
Day	-14 to –1	1	2	3	4	1	8	15	1	8	15	1	1	1	N/A	N/A
Visit Window (compared to Day 1)	N/A	N/A				* [b]	±2 days	±2 days	±2 days	±2 days	±2 days	±1 wk	±1 wk	±1 wk	N/A	±7 days (compared to trt disc visit)
Vital signs (resting blood pressure, pulse rate, body temperature) including weight and height [e]	X [e]	X	X			X	X	X	X			X [i]	X	X [i]	X	(X) [j]
Clinical chemistry/haematology	X	X	X			X	X	X	X	X [k]	X [k]	X	X	X	X	(X) [l]
Urinalysis [m]	X	X	X			X	X	X	X			X	X	X	X	
Pregnancy test (pre-menopausal females only)	X	X											X			
PK blood sampling for AZD6244 [n]		X	X	X	X	X	X									
Troponin I	X											X		X		
ECG [o]	X	X				X			X			X [i]		X [i]	X	(X) [j]
WHO performance status	X								X			X	X	X	X	
Echocardiogram/MUGA [i]	X [p]											X		X		(X) [j]
Tumour evaluation by RECIST [q]	X [r]											X		X	X	
Physical examination	X [s]												X		X	

Table 4 Study plan (Monotherapy Part)

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14+** [a]	Discontinuation from treatment	
Visit Description	Screening	Treatment Period													Treatment Discontinuation Visit	28 days post last dose of last study treatment
Cycle		0				1			2			3	4	5		
Day	-14 to –1	1	2	3	4	1	8	15	1	8	15	1	1	1	N/A	N/A
Visit Window (compared to Day 1)	N/A	N/A				* [b]	±2 days	±2 days	±2 days	±2 days	±2 days	±1 wk	±1 wk	±1 wk	N/A	±7 days (compared to trt disc visit)
Ophthalmologic examination [t]	X											X				(X) [j]
AZD6244 dosing [u]		X Single dosing	(wash-out)			twice-daily dosing →										
Check returned study medication									X			X	X	X	X	

a From Visit 14 onwards patients to attend clinic visits every 3 weeks until discontinuation of treatment with assessments matching those at visit 14, with the exception of Troponin I (not assessed at any further scheduled visits, only assessed on occurrence of any cardiorespiratory event with no obvious diagnosis), RECIST assessments (see Section 18.1), echocardiogram(MUGA)/single ECG (every 12 weeks), pregnancy test (every 9 weeks from Visit 13) and physical examination (every 9 weeks from visit 13).

b To schedule the visit date for Visit 7 or thereafter based on the starting date of Cycle 1.

c Another informed consent should be obtained from patients before the start of Cycle 2 (see Section 9.1).

d The tumour sample collected can be the original diagnostic tumour specimen, or a more recent archival tumour specimen collected pre-study. Optional fresh biopsy will be taken at the time of documented progression.

e Height will be measured only at screening.

f **Consenting patients only (separate consent required for genetic analysis).** If a patient agrees to participate in the host pharmacogenetics research component of the study (by signing the optional Pharmacogenetics research consent), a 10 mL blood sample will be collected. This should be taken once the patient has been enrolled into treatment. Since DNA is a stable parameter, this sample may be taken at other times on the study.

g **Optional biomarker blood sample (separate biomarker consent required prior to taking sample).** Blood samples (1 x 4 mL and 1 x 10 mL) will be taken to provide serum and plasma respectively at each time-point. The blood samples will be taken at screening, pre-treatment on Day 1, Day 8 of Cycle 1, Day 1 of Cycle 2, Day 1 of Cycle 3, pre-dose Day 1 of alternate other cycle and at discontinuation of therapy.

h All cardiorespiratory AEs with no obvious diagnosis should be assessed with an echocardiogram/MUGA, single ECG, vital signs, weight and blood samples for Troponin I taken at the time of the event. Asymptomatic decreases in LVEF should be investigated according to the algorithm provided in Appendix K. All new dyspnoea AEs or worsening of pre-existing dyspnoea AEs should be followed up according to the dyspnoea algorithm provided in Appendix J. If a patient experiences an AE of visual disturbance (including blurring of vision) a complete full ophthalmological examination, including a slit-lamp examination, must be performed (See Section 12.3.11.4).

i Vital signs (including weight) and single ECG must be repeated each time an echocardiogram/MUGA is performed and as described in footnote h. These assessments should not be repeated during the relevant visit if already performed as part of the echocardiogram/MUGA procedure.

j Patients who have a drop in LVEF >10% percentage points from baseline at time of discontinuation of AZD6244 should have a follow up echocardiogram/MUGA, single ECG and vital signs (including weight) performed 28 days after discontinuation of AZD6244 in order to document reversibility. Patients who have a retinal abnormality prior to discontinuation of AZD6244 should, if practicable, have a follow up eye examination performed 28 days after discontinuation of AZD6244 in order to document reversibility (See Section 12.3.6).

k Haematology samples only to be collected 7 days and 14 days after Cycle 2.

l All patients with an AST, ALT or bilirubin value > ULN at time of the last dose of AZD6244 should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 28 days (±7 days) after permanent discontinuation of AZD6244.

m For urinalysis, a single-spot early morning urine specimen will be collected on the day of the scheduled visit, where the local laboratory is able to determine urine albumin and urine creatinine concentrations from a single-spot urine specimen.

n Blood samples for AZD6244 PK to be collected on Cycle 0/Day 1, Day 2, Day 3 and Day 4, and Cycle 1/Day 1 and Day 8. See Table 5 for complete schedule.

o Single ECG at Visit 1, treatment discontinuation visit and each time an echocardiogram/MUGA is performed; triplicate ECGs pre-dose, 2 hours and 4 hours post-dose of AZD6244 at Visit 2 and Visit 6, and 2 hours post-dose of AZD6244 at Visit 9.

p Baseline echocardiogram/MUGA can be performed up to 28 days prior to enrolment.

q RECIST assessment will be performed using CT or MRI scans of chest and abdomen, including liver and adrenal glands. Any other areas of the disease involvement should be additionally investigated based on signs and symptoms of individual patients. Follow-up assessments will be performed at week 6 (±1 week), week 12 (±1 week), week 18 (±1 week), week 24 (±1 week), then every 12 weeks (±1 week), and treatment discontinuation relative to start of study treatment until objective disease progression by RECIST 1.1. Any other sites at which new disease is suspected should also be appropriately imaged.

r Baseline CT or MRI scans can be performed up to 28 days prior to start of study treatment.

s Physical examination to occur every 9 weeks (relevant to Day 1).

t Full ophthalmological examination should include a slit-lamp examination (See 12.3.11.4).

u Patients will receive AZD6244 for as long as, in the opinion of the investigator, they are receiving clinical benefit in the absence of significant toxicity. Patients should continue to receive AZD6244 until at least RECIST defined progression.

Table 5 PK sample collection AZD6244

Study Day	Time
C0/ D1	Pre-dose (within 10 minutes prior to dosing)
	30 min[a]
	1 h[a]
	1 h and 30 min[a]
	2 h[a]
	4 h[a]
	8 h[a]
	12 h[a]
C0/ D2	24 h[a]
C0/ D3	48 h[a]
C0/ D4	72hr[a]
C1/ D1	Pre-dose (within 10 minutes prior to dosing)
	30 min[a]
	1 h[a]
	1 h and 30 min[a]
	2 h[a]
	4 h[a]
	8 h[a]
	12 h[a]
C1/ D8	Pre-dose (within 10 minutes prior to dosing)
	30 min[a]
	1 h[a]
	1 h and 30 min[a]
	2 h[a]
	4 h[a]
	8 h[a]
	12 h[a]

a Relative to time of dose of AZD6244

12.2 Recording of data

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

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and for the provision of answers to data queries according to the applicable information.

The investigator will sign the completed Case Report Forms. A copy of the completed Case Report Forms will be archived at the study site.

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

The investigator will record data on the observations, tests and assessments specified in the protocol on the electronic CRFs provided by AstraZeneca. The CRF will be accompanied with 'Instructions for the investigator', which should be followed. These instructions provide guidance for the recording of study data in the CRF including how to change data incorrectly recorded.

12.3 Safety procedures

The primary study variable is safety. The following study measurements will be obtained at various time points throughout the study. The times of these measurements are detailed in the study plans (Section 12.1).

- ECG
- Vital signs (including weight)
- Physical examination
- Safety assessments (clinical chemistry, hematology, urinalysis, etc)
- Echocardiogram/MUGA
- Troponin I
- Ophthalmologic examination

12.3.1 Enrollment and screening (Visit 1)

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

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

The registration centre manages and keeps the registration code centrally and electronically. The name and contact of centre are as follows:

Name: AZD6244 Registration Centre

Office hours: 9:30 - 17:30, Mon - Fri

(Closed on Sat and Sun, national holidays, 29 Dec - 4 Jan)

E-code (EXXXXYYY) consists of a 4-digit centre number (XXXX) and a 3-digit serial number (YYY, starting with 001) issued by each study centre in order of informed consent taken. For centre number, see Supplement A "Investigators and Study Administrative Structure".

The investigator(s) fill in the "Enrolment Notification Form" after the written informed consent is obtained, and send the form to the AZD6244 Registration Centre by fax. The registration centre records the information on the enrolment list which is maintained in registration centre and send the "Enrolment Confirmation Form" to the investigator(s) by fax.

The investigator(s) send the "Registration Notification Form" to the registration centre by fax (both eligible and ineligible) after confirming of the patient's eligibility. The registration centre confirm the patient eligibility and send the "Registration Confirmation Form" to the investigatr(s) by fax with the registration number when the patient is eligibile.

The registration number is a 3-digit serial number, ie, starting with the following numbers for each dose.

Cohort	Registration number
1	101, 102, 103…
2	201, 202, 203…
3	301, 302, 303...
4	401, 402, 403...

If a patient is not evaluable for the dose escalation, an additional patient could be entered in that dose level.

Each patient will undergo screening (see Study Plan Table 4) during the 14 days prior to admission to confirm eligibility (see Sections 10.1 and 10.2). Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided

the assessments fall within the protocol specified period prior to the first dose of study treatment. Once all criteria for eligibility have been checked, and the patient fulfils all the inclusion and none of the exclusion criteria, the patient is then eligible to receive AZD6244.

The screening will consist of:

- Demography (date of birth, sex, race)
- Collection of AEs will start after signing the first consent form.
- Main study informed consent will be obtained prior to all other study procedures including consent for access to the original archival diagnostic tumour or a more recent archival biopsy.
- Optional consent for blood samples for biomarker analysis, and optional consent for a fresh biopsy to be taken at documented progression of the patient.
- Optional consent for blood sample for pharmacogenetics.
- The following patient background information will be collected for each patient:
  - Histological/cytological confirmation of NSCLC
  - Disease staging
  - Medical and surgical history, concomitant disease
  - Concomitant medications and previous anti-cancer therapy
  - Smoking status
- Tumour evaluation according to RECIST 1.1. guidelines using CT or MRI of the chest and abdomen including liver and adrenal glands must have been performed up to 28 days prior to first study treatment. Any other areas of the disease involvement should be additionally investigated based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 4 weeks before start of treatment
- Assessment of WHO performance status
- Physical Examination
- Vital signs (resting blood pressure (BP), pulse rate, body temperature), weight and height
- Blood samples for clinical chemistry and haematology

- Blood samples for Troponin I
- Blood samples for biomarker analysis (optional)
- Urinalysis
- Pregnancy test for female pre-menopausal patients
- Single ECG
- Full ophthalmologic examination, including slit-lamp examination
- Echocardiogram (can have been performed up to 28 days prior to first study treatment)/MUGA
- For those patients who agree to have original archival diagnostic tumour or a more recent archival biopsy, informed consent will be obtained and a pre-dose tumour sample collected. (for details see Appendix I)

12.3.2 Visit 2, Cycle 0 Day 1

During this visit eligible patients will be enrolled into the study to commence treatment with AZD6244 single dosing.

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

Prior to dosing the patients will undergo the following assessments and procedures:

- Collection of AEs
- Changes to concomitant medications
- Vital signs (resting BP, pulse rate, body temperature) and weight
- Triplicate ECGs (within 5 mins) pre-dose, 2 hours and 4 hours post-dose of AZD6244
- Pre-dose PK sample (within 10 minutes prior to dosing) with subsequent samples taken at 0.5, 1, 1.5, 2, 4, 8 and 12 hours post-dose of AZD6244
- Blood samples for clinical chemistry and haematology
- Urinalysis
- Pregnancy test for female pre-menopausal patients

- For those patients who agree to have a blood sample stored for future host genetic analysis, host genetics research informed consent will be obtained and a pre-dose blood sample collected (for details see Appendix H)

- AZD6244 single dosing will be administered orally to all patients on Visit 2, Cycle 0 Day 1.

12.3.3 Follow-up visits (Visit 3, Cycle 0 Day 2 – onwards until discontinuation)

Patients will attend follow-up visits. At each of these visits patients will undergo the following assessments:

- Collection of AEs. Please note:

  - All cardiorespiratory AEs with no obvious diagnosis should be assessed with an echocardiogram/MUGA, single ECG, vital signs (resting BP, pulse rate, body temperature), weight and blood samples for Troponin I taken at the time of the event

  - Asymptomatic decreases in left ventricular ejection fraction (LVEF) should be investigated according to the algorithm provided in Appendix K

  - All new dyspnoea AEs or worsening of pre-existing dyspnoea AEs should be followed up according to the dyspnoea algorithm provided in Appendix J

  - If a patient experiences an AE of any visual disturbance (including blurring of vision) a complete ophthalmologic examination, including slit-lamp examination, must be performed.

- Changes to concomitant medications

- Blood samples for clinical chemistry and haematology on Cycle 0 Day2, Cycle 1 Day 1, Day 8 and Day 15, Cycle 2 Day1 and every 3 weeks thereafter. Note: only haematology samples must be collected 7 days and 14 days after Cycle 2 (Cycle 2 Day 8 & Day 15).

- Blood samples for biomarker analysis (optional) will be taken at pre-dose on Day 1, Day 8 of Cycle 1, Day 1 of Cycle 2, Day 1 of Cycle 3 and pre-dose Day 1 of alternate other cycle.

- To all patients, on cycle 1 Day 1 (Visit 6) twice-daily dose of AZD6244 will be initiated and given continuously on a twice daily basis.

Additional assessments will be performed as follows:

- RECIST evaluations using CT (or MRI) of chest and abdomen (including liver and adrenal glands) to be performed at week 6, week 12, week 18, week 24, and every 12 weeks thereafter relative to date of Cycle 1 Day 1.

- Vitals signs (resting BP, pulse rate, body temperature) and weight on Cycle 0 Day 2 and Cycle 1 Day 1, Day 8, Day 15, Cycle 2 Day 1 and every 3 weeks thereafter (please note that vital signs should not be repeated if they have already been taken at the time of the echocardiogram at the same visit)

- Urinalysis on Cycle 0 Day 2, Cycle 1 Day 1, 8, 15, Cycle 2 Day 1 and every 3 weeks thereafter

- Triplicate ECGs (within 5 mins) pre-dose, 2 hours and 4 hours post-dose of AZD6244 on Cycle 1 Day 1, and 2 hours post-dose of AZD6244 Cycle 2 Day 1. Single ECG on Cycle 3 Day 1, Cycle 5 Day 1 and every 12 weeks thereafter will also be recorded at the time of every echocardiogram assessment.

- PK blood sampling for AZD6244 (during Cycle 0): Subsequent PK samples taken at 24 hours, 48 hours, 72 hours post-single dose of AZD6244 on Cycle 0 Day 1.

- PK blood sampling for AZD6244 (Cycle 1): Pre-dose PK sample (within 10 minutes prior to dosing) with subsequent samples taken at 0.5, 1, 1.5, 2, 4, 8 and 12 hours post-dose of AZD6244 on Cycle1 Day 1 and Cycle 1 Day 8. Patients must withhold taking the morning dose of AZD6244 until pre-dose PK sample is collected.

- Assessment of WHO performance status on Cycle 2 Day 1, Cycle 3 Day 1 and at every scheduled visit thereafter

- Check AZD6244 returned medication on Cycle 2 Day 1 and at every scheduled visit thereafter

- Echocardiogram/MUGA on Cycle 3 Day 1, Cycle 5 Day 1 and every 12 weeks thereafter, and treatment discontinuation. Vital signs (resting BP, pulse rate, body temperature) and weight and a single ECG must also be recorded at the time of every echocardiogram assessment.

- A full ophthalmologic examination will be performed on Cycle 3 Day 1 and on occurrence of any AE of any visual disturbance (including blurring of vision)

- Blood samples for Troponin I will be taken on Cycle 3 Day 1 and Cycle 5 Day 1, and on occurrence of any cardiorespiratory event with no obvious diagnosis

- Physical examination will be performed every 9 weeks relevant to Cycle 1 Day 1 of the study whilst patients are receiving AZD6244 monotherapy (eg, week 9, week 18 and every 9 weeks thereafter).

- Pregnancy test for female pre-menopausal patients performed on Cycle 4 Day 1 and every 9 weeks thereafter.

Patients will be permitted to continue to receive any study treatment after objective disease progression if, in the opinion of the investigator, they are continuing to derive clinical benefit from study treatment, in the absence of significant toxicity.

12.3.4 Treatment discontinuation visit

The treatment discontinuation visit will be conducted as soon as possible after the patient received the last dose of study drug. This will be after the last dose of AZD6244.

During this visit patients will undergo the following assessments:

- RECIST evaluations using CT (or MRI) of chest and abdomen (including liver and adrenal glands)
- Assessment of WHO performance status
- Vital signs, (resting BP, pulse rate, body temperature) and weight
- Physical examination
- Blood samples for clinical chemistry and haematology
- Blood samples for biomarker analysis (optional)
- Urinalysis
- Single ECG
- Collection of AEs
- Changes to concomitant medications
- Check returned AZD6244
- Collection of optional fresh tumor samples

Following discontinuation of AZD6244 for any reason, patients may receive any subsequent therapy for solid malignancies at the discretion of the investigator. Details of such treatment (including surgery) are to be recorded in the eCRF.

Collection of AEs/SAEs will continue until 28 days after the last dose of the last study treatment. 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 eCRF.

12.3.5 28 days after last dose of last study treatment

Twenty-eight (28) days (±7 days) after permanent discontinuation of the study treatment (AZD6244) a treatment discontinuation follow-up contact should be performed to collect the following for all patients:

- AEs
- Changes to concomitant medications (following this visit, only anti-cancer treatment [including surgery] will be collected).

12.3.6 Additional assessments 28 days after last dose of AZD6244

Twenty-eight (28) days (±7 days) after the last dose of AZD6244 has been taken, the following assessments should be performed, where necessary:

- All patients with an AST, ALT or bilirubin value above upper limit of normal (ULN) at time of the last dose of AZD6244 should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed.
  NB. In case a patient shows an AST or ALT ≥ 3 x ULN or total bilirubin ≥ 2 x ULN please refer to Appendix N 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law' for further instructions.
- Patients who have a drop in LVEF >10% percentage points from baseline at time of discontinuation of AZD6244 should have a follow up echocardiogram/MUGA, single ECG and vital signs (include weight) performed in order to document reversibility.
- Patients who have a retinal abnormality prior to discontinuation of AZD6244 should, if practicable, have a follow up eye examination performed 28 days after discontinuation of AZD6244 in order to document reversibility.

12.3.7 Laboratory safety assessment

The following clinical chemistry, haematology and urinalysis tests will be performed:

Table 6 Laboratory safety assessments (Monotherapy Part)

Clinical chemistry	Haematology	Urinalysis [a]
s-Albumin	Erythrocyte count	u-Albumin
s-ALT	Haemoglobin	u-Creatinine
s-AST	Platelet count	
s-ALP	Leucocyte cell count	
s-Total Calcium	Leucocyte differential count (absolute count):	
s-Creatinine	Neutrophils	

Table 6 Laboratory safety assessments (Monotherapy Part)

Clinical chemistry	Haematology	Urinalysis [a]
s-Gamma glutamyl transferase (γGT)	Eosinophils	
s-Glucose	Basophils	
s-Magnesium	Lymphocytes	
s-Phosphate	Monocytes	
s-Potassium		
s-Sodium		
s-Total protein		
s-Total bilirubin		
s-Urea nitrogen		
s-Troponin I		

a To be performed at sites where the local laboratory is able to determine urine albumin and urine creatinine concentrations from a single-spot specimen
s serum
u urine

All the laboratory safety assessments will be analysed by the local laboratory.

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

For blood volume see Section 17.1.

A single-spot early morning urine specimen will be collected on the day of scheduled visit., at sites where the local laboratory is able to determine the concentration of urine albumin and urine creatinine from a single-spot urine specimen. Investigational sites unable to report these parameters will perform routine urinalysis according to the local standard of care.

12.3.8 Physical examination

A physical examination will be performed at screening and every 9 weeks relevant to Cycle 1 Day 1 of the study whilst patients are receiving AZD6244 (eg, week 9, week 18 and every 9 weeks thereafter).

The last physical examination in the study will be performed at treatment discontinuation visit.

12.3.9 ECG

ECGs will be analysed locally. Patients should be supine and at rest 10 minutes prior to recording the ECG.

Parameters including heart rate, duration of QRS complex, R-R, PR and QT intervals will be collected. QTcF will be calculated by AstraZeneca from the data provided.

The investigator should review the paper copy of the ECGs on each study day and may refer to a local cardiologist if appropriate.

Any symptoms from the patient should be registered as a comment and if AE criteria are met, recorded as an AE.

12.3.9.1 Screening ECG

At screening all patients will have a single 12-lead ECG performed. The screening ECG can be conducted up to 14 days prior to Cycle 0 Day 1.

12.3.9.2 Treatment Phase ECGs

Patients will have 12-lead ECGs captured in triplicate (within 5 mins) pre-dose, 2 hours and 4 hours post-dose of AZD6244 on Cycle 0 Day 1, Cycle 1 Day 1 and 2 hours post-dose of AZD6244 on Cycle 2 Day 1. Single ECGs must also be performed at the time of every echocardiogram assessment and on occurrence of any cardiorespiratory adverse event. A single ECG is also required at discontinuation of treatment.

12.3.10 Vital signs

Resting blood pressure and pulse rate will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size. Vital sign assessments, including weight, will be performed at screening, Cycle 0 Day 1, Cycle 0 Day 2, Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1 and then 3 weekly thereafter, at discontinuation of the last study treatment, and at the time of any echocardiogram assessment. Height will be assessed at screening only.

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

12.3.11 Other safety assessments

12.3.11.1 Pregnancy test

A pregnancy test will be performed at screening, prior to starting treatment at Cycle 0 Day 1, from thereafter at Cycle 4 Day 1 and 9 weekly thereafter for female pre-menopausal patients.

12.3.11.2 Echocardiogram/MUGA

An echocardiogram will be conducted at screening (can be performed up to 28 days prior to first study treatment) and on Cycle 3 Day 1, Cycle 5 Day 1 and at 12 weekly intervals on treatment. A further echocardiogram should be performed as part of the assessment package for any cardiorespiratory adverse event with no obvious diagnosis (eg, not mandated in case of confirmed pulmonary embolus or myocardial infarction).

Left ventricular ejection fraction (LVEF), end diastolic and end systolic left ventricular diameters should be recorded at each echocardiogram assessment. Patients experiencing an

asymptomatic but clinically significant drop in LVEF should be managed according to the algorithm provided in Appendix K. Patients who have a drop in LVEF >10% percentage points from baseline at time of discontinuation of AZD6244 should have a follow-up echocardiogram performed 28 days after permanent discontinuation of AZD6244 in order to document reversibility.

12.3.11.3 Troponin I

Blood samples for Troponin I will be collected at screening and on Cycle 3 Day 1, Cycle 5 Day 1 and in cases of any cardiorespiratory AEs with no obvious diagnosis and will be sent to a laboratory for analysis.

12.3.11.4 Ophthalmologic examination

A complete ophthalmologic examination including a slit-lamp examination must be performed at screening, on Cycle 3 Day 1 and when a patient experiences a visual disturbance AE (including blurring of vision). The ophthalmologic examination will include assessment of visual acuity, a slit-lamp examination, measurement of intraocular pressure and funduscopy.

Combination Therapy and Monotherapy Part: Common Section From 13

13. ADVERSE EVENTS

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

13.1 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 (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

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

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

13.2 Definitions of serious adverse events

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to adverse events), except hospitalisation that has been planned before enrolment
- Results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions

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

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

For definition of other significant adverse events (OAE) see Section 19.3.2.

13.3 Recording of adverse events

Time period for collection of adverse events

AEs will be collected throughout the study, from informed consent until the end of the follow-up period. The follow-up period is defined as 28 days after investigational prooduct and/or docetaxel is discontinued. SAEs occurring in the follow-up period should be reported to AstraZeneca in the usual manner (see Section 13.4).

Follow-up of unresolved adverse events

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

If an investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to AZD6244, the investigator should notify AstraZeneca.

Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date when the AE started and stopped
- CTCAE grade maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- Outcome

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

Severity of AE

For each episode on an adverse event, all changes to the CTCAE grade attained as well as the highest attained CTCAE grade should be reported.

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 13.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

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

Causality collection

The investigator will assess causal relationship between investigational product and each adverse event, and answer 'yes' or 'no' to the question: 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

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

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarised in the Clinical Study Report. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the criteria for a SAE, a DLT or are the reason for discontinuation of treatment with the

investigational product unless clearly due to progression of disease under study (see Disease progression).

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

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

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

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

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. **Events that are unequivocally due to disease progression should not be reported as AEs during the study.**

New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

Handling of deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of investigational product, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the CRF module, but should not be reported as a SAE during the study

- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the study monitor as an SAE within 24

hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes

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

13.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives promptly, 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 AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE promptly, or **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness is Section 5.4 of the Investigators' Brochure for AZD6244.

14. PHARMACOKINETICS

14.1 Collection of pharmacokinetic samples

Venous blood samples (2 mL, sampling tube with ETDA-2K) for determination of plasma concentrations of AZD6244 and its metabolites (N-desmethyl AZD6244 and AZD6244 amide), and another set of PK samples (2 mL of venous blood, sampling tube with ETDA-2K) for determination of docetaxel concentrations in plasma will be taken at the times presented in Table 2 and Table 5. The deviation of timing of blood sampling will not be handled as protocol deviation. Samples will be collected, labeled, stored, and shipped as detailed in Laboratory Manual.

The total number of samples and the total volume of blood taken from each patient will not exceed that presented in Section 17.1, Table 7.

14.2 Determination of drug concentration in pharmacokinetic samples

Samples for determination of AZD6244 and its metabolites, and/or docetaxel concentrations in plasma will be analysed by on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest (ie, AZD6244, N-desmethyl AZD6244, AZD6244 amide and docetaxel) at the time of receipt by the bioanalytical laboratory will be analysed.

15. PHARMACODYNAMICS (NOT APPLICABLE)

Not applicable.

16. EXPLORATORY RESEARCH

16.1 Exploratory biomarker research

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

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

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

16.1.1 Collection of archival tumour samples

All patients will be asked to provide consent to supply a sample of their original diagnostic archival tumour blocks (or a more recent archival tumour sample if one has been taken after diagnosis and prior to study start). If a sample is not available this will not prevent the patient from participating in the study.

The pre-study tumour samples will preferably be in the form of a formalin fixed paraffin embedded block (tissue derived from the diagnostic tumour or a metastatic site). If this is not possible, freshly prepared unstained sections from the archival tumour block may be provided.

Patients will also be asked to provide an optional tumour biopsy at progression to allow for exploratory research to understand resistance mechanisms.

Planned analysis for the tumour samples will be as follows:

- *KRAS* mutation status, *p53*, *LKB1* and *EGFR*, etc.

Further details are included in the laboratory manual.

16.1.2 Collection of exploratory blood-borne biomarkers

Exploratory biomarker research samples

Blood samples (4 mL x 1 and 10 mL x 1) will be taken to provide serum and plasma respectively at each time-point.

The blood samples will be taken at screening, pre-dose on Day 1, Day 8 of Cycle 1, Day 1 of Cycle 2, Day 1 of Cycle 3, pre-dose Day 1 of alternate cycles and at discontinuation of therapy. The samples will be analysed for a range of biomarkers which may correlate with drug response (ie, predictive or resistance markers).

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

16.2 Pharmacogenetics

If a patient agrees to participate in the host pharmacogenetics research component of the study (by signing the optional Pharmacogenetics research consent), a 10 mL blood sample will be collected. This should be taken once the patient has been enrolled into treatment. Since DNA is a stable parameter, this sample may be taken at other times on the study.

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

16.2.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from the patients immediately prior to dosing (single dose day). Although genotype is a stable parameter, early sample collection is

preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event. Such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn prior to dosing it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study.

17. BIOLOGICAL SAMPLING PROCEDURES

17.1 Volume of blood

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

Table 7 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	5	7	35
	Haematology	2.6	9	24[a]
Pharmacokinetic				
AZD6244 monotherapy		2	27	54
AZD6244 + docetaxel combination therapy		2	35	70
Biomarker Serum sample		4	4	16
Biomarker Plasma sample for CFDNA		10	4	40
Troponin I		2	1	2
Host genetics (optional)		10	1	10
Total				
AZD6244 monotherapy			53	181
AZD6244 + docetaxel combination therapy			61	197

a The amount is rounded up.

The total volumes of blood given in Table 7 are based upon a patient remaining in the study for screening period, Cycle 0 (4 days), Cycle 1 (3 weeks) and Cycle 2 (3 weeks). At each 3-weekly visit after this a further 7.6 mL of blood will be taken for clinical chemistry and haematology. At every 6 weeks, 14 mL and 2 mL blood samples will be taken for biomarker and Troponin I respectively. In addition, on occurrence of all cardiorespiratory AEs with no obvious diagnosis, a 2 mL blood sample will be taken to assess Troponin I. In addition, on occurrence of treatment discontinuation, a 7.6 mL blood sample will be taken for clinical chemistry and haematology, and 14 mL blood samples will be taken for biomarker. Clinical

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

17.2 Handling, storage and destruction of biological samples

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

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. Samples may also be disposed of earlier, pending further notification.

Biological samples for future research can be retained at AstraZeneca/CRO, on behalf of AstraZeneca for a maximum of 25 years following the last patient's last visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in a Clinical Study Report Addendum/Scientific Report or Scientific Publication.

17.2.1 Pharmacokinetic samples

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.

17.2.2 Samples for exploratory research (germline genetic analysis)

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

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

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping 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.

17.3 Labelling and shipment of biohazard samples

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

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

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

17.4 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.

17.5 Withdrawal of informed consent for donated biological samples

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

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

The Principal Investigator:

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

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

- Ensures that the patient and AstraZeneca are informed about the sample disposal

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

18. ANTI-TUMOUR ACTIVITY

18.1 Tumour assessments

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

The methods of assessment of tumour burden used at baseline CT or MRI of the chest and abdomen including liver and adrenal glands must be used at each subsequent follow-up assessment. Any other areas of the disease involvement should be additionally investigated based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 4 weeks before start of treatment, and ideally should be performed as close as possible to the start of study treatment.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments at 6 weeks ± 1 week, 12 weeks ± 1 week, 18 weeks ± 1 week, 24 weeks ± 1 week, and then every 12 weeks ± 1 week until objective disease progression as defined by RECIST 1.1. Any other sites at which new disease is suspected should be appropriately imaged.

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

For patients who only have non-measurable disease at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 guidelines for response for NTLs: CR, PD and Non CR/Non PD.

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

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit

discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Section 6.1 / 12.1 and Appendix F, Section 4.1.

19. EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS

19.1 Definition of study endpoints

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

- Safety and Tolerability (Primary)
- AZD6244 pharmacokinetics (Secondary)
- Tumour response (Exploratory)

Safety endpoints are defined in Section 13. Derivations, calculations and analysis plans for each of these endpoints are presented below.

19.2 Determination of sample size

The primary objective of this study is to investigate the safety and tolerability and thereby identify the tolerable doses of AZD6244 monotherapy and of AZD6244 + docetaxel combination therapy, and to recommend dose(s) for evaluation in future clinical studies. Hence the number of patients has been based on the desire to obtain adequate tolerability, safety and pharmacokinetic data while exposing as appropriate number of targt patient populations as possible close to phase II/III studies.

For the monotherapy and a dose finding phase (Part A) of combination therapy, cohorts of 3-6 evaluable patients will be required. The total number of patients will depend upon the number of dose escalation / reductions of the investigational product.

If study proceed to a dose expansion phase (Part B) of the combination therapy, up to an additional 12 evaluable patients will be accrued at a selected combination dose regimen to refine further the tolerability, pharmacokinetics and biological activity.

19.3 Calculation or derivation of safety variables

19.3.1 Vital signs, laboratory data, ECGs, echocardiogram, physical examination and ophthalmologic examination

For change from baseline summaries for vital signs, laboratory data, ECGs, echocardiogram, physical examination and ophthalmologic examination, the baseline value will be the latest

result obtained prior to the start of study treatment. Change from baseline will be calculated programmatically by AstraZeneca using absolute change from baseline.

QTcF (Fredericia) will be calculated programmatically by AstraZeneca using the reported ECG values (heart rate).

The urinary albumin/creatinine ratio (mg/mmol) (UACR) will be calculated by AstraZeneca.

Corrected Calcium and Calcium Phosphate product will be calculated programmatically by AstraZeneca 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.

Data from physical examinations and ophthalmologic examinations will be listed and not summarised.

19.3.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of investigational product. Based on the expert's judgement, adverse events of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the Clinical Study Report. A similar review of laboratory values, vital signs, ECGs and other safety assessments will be performed for identification of other significant adverse events.

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

19.4 Calculation or derivation of pharmacokinetic variables

Where data allow, the following PK parameters will be determined following administration of AZD6244 alone (Cycle 0, Day 1), following administration of AZD6244 and docetaxel together (Cycle 1, Day 1) and following twice daily administration of AZD6244 (Cycle 1, Day 8). Additional parameters may be determined if deemed appropriate.

- Cycle 0, Day 1
  AZD6244 and its metabolites: C_{max}, t_{max}, $AUC_{(0-12)}$, $AUC_{(0-t)}$, AUC, $t_{½}$
  AZD6244 only: CL/F

- Cycle 1, Day 1
  AZD6244, metabolites and docetaxel: C_{max}, t_{max}, $AUC_{(0-12)}$

- Cycle 1, Day 8
  AZD6244 and its metabolites: C_{max}, t_{max}, $AUC_{(0-12)}$, R_{AC}

The parameters above will be derived using a noncompartmental analysis as follows: The maximum plasma concentrations (C_{max}) and the time to reach the maximum plasma concentrations (t_{max}) will be determined by visual inspection of the plasma concentration-time profiles. The area under the plasma concentration-time curve from zero to 12 hours post-dose, $AUC_{(0-12)}$, will be calculated by the linear trapezoidal rule. Where more than one maximum occurs, the reported value will be assigned to the first occurrence. For the first single dose, the area under the plasma concentration-time curve from zero to the time of the last quantifiable plasma concentration, $AUC_{(0-t)}$, will also be calculated by the linear trapezoidal rule and the area from the last quantifiable drug concentration to infinite time, AUC, will be calculated by the following formula:

$AUC_{(0-t)} + C_t/\lambda_z$, where C_t is the last quantifiable concentration and λ_z is the terminal rate constant, calculated by log-linear regression of the terminal portion of the concentration-time profile where there are sufficient data (ie, there are at least 3 points in the terminal phase). The terminal half-life ($t_{½}$) will be calculated from the equation $Ln(2)/\lambda_z$. If the data allows, the clearance (CL/F for oral administration) will be calculated

For the multiple dose, extent of accumulation (R_{AC}) will be calculated as the ratio of the $AUC_{(0-12)}$ on Day 8 of Cycle 1 to the $AUC_{(0-12)}$ on Day 1 of Cycle 1.

19.5 Calculation or derivation of pharmacodynamic variables (Not applicable)

Not applicable.

19.6 Calculation or derivation of exploratory research variables (Not applicable)

Not applicable.

19.7 Calculation or derivation of tumour response variables

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

Progression of TLs will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

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

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

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

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

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

For the analysis of objective response rate an ‘evaluable-for-response’ population will be derived and will exclude patients who do not have measurable disease at baseline.

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

In the case of stable disease, measurements should have met the stable disease criteria at least once after the study start.

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

Best overall response will be calculated as the best response recorded from date study treatment started for each patient. Objective response rate (ORR) is defined as the percentage of patients who have a confirmed CR or PR prior to any evidence of progression (as defined by RECIST 1.1).

A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.

Percentage change in tumour size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs.

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

19.8 Description of analysis sets

The analysis of data will be based on different subsets according to the purpose of the analysis. Throughout the safety results sections, erroneously treated patients (eg, those assigned to receive dose A who actually received dose B, those who failed to meet the selection criteria) will be accounted for in the actual dose group received.

Analysis sets are presented in Table 8 and Table 9.

Table 8 Analysis sets (Combination Therapy Part)

Analysis Set	Definition
Safety	All patients who received at least 1 dose of AZD6244.
Pharmacokinetics	Dosed patients for whom an adequate PK profile has been obtained.
Evaluable for combination regimen dose escalation (Part A)	See Section 5.1.3.
Tumour response	Dosed patients with a baseline tumour assessment.

Table 9 Analysis sets (Monotherapy Part)

Analysis Set	Definition
Safety	All patients who received at least 1 dose of AZD6244.
Pharmacokinetics	Dosed patients for whom an adequate PK profile has been obtained.
Evaluable for monotherapy regimen dose escalation	See Section 11.1.3.
Tumour response	Dosed patients with a baseline tumour assessment.

19.9 Methods of statistical analysis

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

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

Demographic data

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

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

Exposure

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

Total exposure and total time on study (date of last dose minus date of first dose +1) will be summarised by the following: mean, standard deviation, minimum, maximum, median and number of observations. In addition, the number and percentage of patients with at least one dose interruption/dose delay and at least one dose reduction will be presented separately for the initial period of evaluability defined as 25 days (4 days for single dosing + 21 days after multiple dosing) and for any time following this initial period of the study.

Safety

Safety data will not be formally analysed. All patients who receive at least one dose of AZD6244 will be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

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

Any AE occurring before the first dose of investigational product (ie, before study Day 1) will be included in the data listings but will not be included in the summary tables of adverse events.

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

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

Details of any deaths will be listed for all patients.

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

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

Pharmacokinetics

Plasma concentrations of AZD6244, its metabolites and docetaxel will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by cohort. Parameters for AZD6244 and its metabolites following single and multiple dosing will be summarised separately. Plasma concentrations at each time point will be summarised according to dose by the following summary statistics:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on a log scale)
- Gmean ± standard deviation (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for AUC, $AUC_{(0-12)}$, $AUC_{(0-t)}$, C_{max}:

- Gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- CV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on a log scale)
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for CL/F, $t_{½}$ and R_{AC}:

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

The following summary statistics will be presented for t_{max}:

- Median
- Minimum
- Maximum
- Number of observations

The pharmacokinetic data for AZD6244 after a single-dose and separately, at steady state will also be displayed graphically. Displays will include plasma concentration patient profiles (on the linear and log-scale) versus time and gmean concentration (± standard deviation) versus time, stratified by dose.

Scatter plots of PK parameters versus dose, or log-dose will also be considered following both single and multiple dose administration of AZD6244 to assess dose proportionality.

Exploratory biomarker research and pharmacogenetics

The data from these research will not form part of the Clinical Study Report (see Section 16).

Tumour response

Tumour response data will be summarised for dosed patients with measurable disease at baseline and separately for dosed patients that only had non-measurable disease at baseline.

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

Waterfall plots (bar charts) indicating the percentage change from baseline in sum of the diameters of TLs will be produced by cohort.

20. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

20.1 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 a SAE and is to be reported as such, see Section 13.4.**

In the case of a medical emergency the investigator may contact the Study Leader. If the Study Leader is not available, contact the Study Physician / other physician at the AstraZeneca KK.

Name	Role in the study	Address & telephone number
	Study Leader	
	Study Physician	

20.2 Overdose

There are no data on overdosing with AZD6244. There is no definition of what constitutes an overdose. There is no known antidote.

Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

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

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

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

For overdoses associated with a SAE, standard reporting timelines apply, see Section 13.4. For other overdoses, reporting should be done within 30 days.

20.3 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to AstraZeneca using the appropriate forms.

20.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy should be followed up and documented even if the patient was withdrawn from the study.

If a pregnancy occurs during exposure to investigational product or in the 6 months (3 months for subjects of monotherapy part) after discontinuing investigational product, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator(s) 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 13.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

20.3.2 Paternal exposure

Pregnancy of a patient's partner is not considered to be an adverse event. However, any conception occurring from the date of dosing until 6 months (3 months for subjects of monotherapy part) after dosing should be reported to AstraZeneca and followed up for its outcome.

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