CLINICAL STUDY PROTOCOL - CONFIDENTIAL

Study Title:	A Phase I, Open-Label Study to Assess the Safety and Tolerability of KU-0059436 in Combination with Carboplatin, KU-0059436 in Combination with a Paclitaxel / Carboplatin (TC) doublet and KU-0059436 in Combination with Paclitaxel in the Treatment of Patients with Advanced Solid Tumours
Protocol Number:	KU36-96
EudraCT:	2007-000939-26
Contract Research Organisation (CRO)	Theradex®
Indication:	Dose Escalation Phase Advanced Solid Tumours Dose Expansion Phase Advanced Ovarian Cancer and Platinum Naïve Metastatic Triple Negative Breast Cancer Randomised Dose Expansion Phase Advanced Ovarian Cancer and Metastatic Breast Cancer
Development Phase:	Phase I
Sponsor:	AstraZeneca AB, 151 85 Södertälje, Sweden
Sponsor's Responsible Medical Officer:	[redacted]

AstraZeneca

SPONSOR PROTOCOL APPROVAL SIGNATURE:

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Signature: [redacted] Date: 29th June 2011

Date of protocol; Final version:	15 February 2007
Date of Amendment 1	21 December 2007
Date of Amendment 2	18 February 2008
Date of Amendment 3	6 May 2008 (Netherlands)
Date of Amendment 4	17 February 2009 (Netherlands)
Date of Amendment 5	15 July 2009 (Netherlands)
Date of Amendment 6	14 June 2010 (Netherlands)
Date of Amendment 7	17 August 2010 (Netherlands)
Date of Amendment 8	10 December 2010 (Netherlands and Belgium)
Date of Amendment 9	23 June 2011 (Netherlands and Belgium)

This study will be conducted according to the principles of Good Clinical Practice as described in International Conference on Harmonisation guidelines, including the archiving of essential documents (CPMP/ICH/135/95)

GENERAL INFORMATION

Study Role	Name	Address
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Study Role	Name	Address
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Data Management and Descriptive Statistics	Theradex®	Theradex® CN 5257 Princeton, New Jersey 08543, USA
Bioanalysis (KU-0059436)	Quotient Bioresearch	Newmarket Road Fordham, Cambridgeshire CB7 5WW UK
Bioanalysis (KU-0059436) (Randomised expansion only)	Covance Laboratories Ltd	Otley Road Harrogate North Yorkshire HG3 1PY UK
Bioanalysis (Total platinum)	Analytico Medinet B.V.C	Bergschot 71 4817 PA Breda Postbus 5510 4801 DM Breda NL
Bioanalysis (Paclitaxel)	BASi	Suite 2, Bldg 500. Abbey Park, Stareton, Kenilworth, Warwickshire CV8 2LY
Pharmacodynamic Analysis	AstraZeneca Pharmaceuticals Any additional centres will be detailed in the laboratory sampling plan	AstraZeneca Pharmaceuticals Tissue Bank Reception, Block 33 Mereside Alderley Park Macclesfield Cheshire SK10 4TG UK

CLINICAL STUDY SYNOPSIS

Name of Sponsor:	**Name of Monitor:**
AstraZeneca AB 151 85 Södertälje, Sweden	Theradex® (Europe) Ltd 7 Pelham Court Broadfield Crawley West Sussex RH11 9SH, UK

Name of finished product: KU-0059436 Gelucire® 44/14 (capsule) and Melt-Extrusion [tablet]

Name of active ingredient: KU-0059436 (also known as olaparib or AZD2281)

Title of the study: A Phase I Open-Label Study to Assess the Safety and Tolerability of KU-0059436 in Combination with Carboplatin, KU-0059436 in Combination with a Paclitaxel / Carboplatin (TC) doublet and KU-0059436 in combination with Paclitaxel in the Treatment of Patients with Advanced Solid Tumours.

Investigators and study centres: See Study Operational Manual

Publication (reference): None

Clinical phase: Phase I

Objectives of the Study

Primary objective

To investigate the safety and tolerability and establish

- Either the dose of KU-0059436 which can be safely administered and which causes inhibition of PARP in combination with an active dose of a paclitaxel / carboplatin (TC) doublet.
- Or the maximum tolerated dose (MTD) of KU-0059436 in combination with paclitaxel / carboplatin (TC) doublet.

Secondary objectives

- To identify the Dose Limiting Toxicity (DLT) of the combination of KU-0059436 and a paclitaxel / carboplatin (TC) doublet.
- To determine the plasma pharmacokinetic profile of;
    - KU-0059436 alone
    - KU-0059436 in combination with carboplatin
    - KU-0059436 in combination with a paclitaxel / carboplatin (TC) doublet
    - KU-0059436 in combination with paclitaxel.
- Randomised Dose Expansion Phase Only: To investigate the effect of food (pre-dose standard meal) on the pharmacokinetics (PK) of oral KU-0059436
- To investigate the pharmacodynamic profile over time in surrogate tissue of KU-0059436 when given in combination with a paclitaxel / carboplatin (TC) doublet.
- To enable a preliminary assessment, in specific patient populations, of the safety and tolerability and anti-tumour activity of up to two dose combinations of KU-0059436 tablet formulation in combination with a paclitaxel / carboplatin (TC) doublet versus KU-0059436 (capsule formulation) at 200 mg bid days1-10 of a 21 day cycle in combination with AUC 4 carboplatin and paclitaxel (175mg/m^2). (Randomised Dose Expansion phase).
- To determine the safety profile of KU-0059436 in combination with paclitaxel given at two dose levels.
- To determine the safety and tolerability profile of the KU-0059436 Melt-Extrusion [tablet] formulation in combination with a paclitaxel /carboplatin (TC) doublet.

Exploratory objective

- To investigate exploratory biomarkers in whole blood, serum, urine and tumour biopsies (on treatment and historical) to ascertain if there are any which differentiate treatment effects, and to investigate their correlation with disease progression/response to therapy or an improved understanding of the disease.

Methodology: Male or female patients with histologically or cytologically diagnosed malignant solid tumours will be recruited to the dose escalation phase of the study, these patients must have had no more than 2 previous platinum based chemotherapy regimens. In the dose escalation phase of the study, up to approximately 180 evaluable patients will be enrolled in the carboplatin and carboplatin / paclitaxel (TC) doublet arms.

Additionally, up to 12 evaluable patients will be enrolled in a comparator and parallel KU-0059436 + weekly paclitaxel dose escalation arm.

Additionally 15 female patients with histologically or cytologically confirmed platinum naïve metastatic triple negative breast cancer and female patients with advanced ovarian cancer will be enrolled into a non-randomised dose expansion of a selected KU-0059436 / carboplatin / paclitaxel combination dose. Breast cancer patients must have had no previous platinum based chemotherapy.

Other doses in the dose escalation phase deemed to be tolerated can be expanded in the non-randomised dose expansion to further assess tolerability. Up to 30 patients in total can be included in these expansions.

A randomised expansion may be implemented to compare up to two selected KU-0059463 (tablet formulation) / carboplatin / paclitaxel dose combination arms versus KU-0059436 (capsule formulation) at 200 mg bid days1-10 of a 21 day cycle in combination with AUC 4 carboplatin and paclitaxel (175mg/m^2). Approximately 45 female patients with histologically or cytologically confirmed measurable metastatic breast cancer and female patients with measurable advanced ovarian cancer, where further treatment with platinum based chemotherapy is indicated, may be enrolled in the randomised dose expansion phase of the study (~15 patients per arm).

Number of patients: Approximately 250 patients.

Diagnosis and main criteria for inclusion:

1. Full-informed written consent.
2. Dose escalation phase:

   Male or female patients with a histologically or cytologically diagnosed malignant solid tumour.

   Non-randomised dose expansion phase:

   Female patients with histologically or cytologically diagnosed metastatic triple-negative breast cancer (platinum naïve) and female patients with histologically or cytologically diagnosed advanced ovarian cancer, where further treatment with platinum based chemotherapy is indicated.

   Randomised dose expansion phase:

   Female patients with histologically or cytologically diagnosed measurable metastatic breast cancer and female patients with histologically or cytologically diagnosed measurable advanced ovarian cancer, where further treatment with platinum based chemotherapy is indicated.

3. **Randomised Dose Expansion Phase Only:** One or more measurable lesions, at least 10 mm in the longest diameter (LD) by spiral CT scan, or 20 mm with conventional techniques, according to RECIST criteria, not irradiated within 12 weeks of the first administration of study drug.
4. Adequate bone marrow, hepatic and renal function including the following:

   a. Haemoglobin ≥10.0 g/dl (6.2mM), absolute neutrophil count ≥1500 x 10^6/L, platelets ≥100,000 x 10^6/L;

   b. Total bilirubin : ≤1.25 x upper normal limit;

   c. AST (SGOT), ALT (SGPT) : ≤2.5 x upper normal limit;

   d. Creatinine: ≤1.5 x upper normal limit.
5. Creatinine clearance (Jaffe or enzymatic serum creatinine) within normal range (>60ml/min).
6. Age ≥18 years.
7. Performance status (PS): ≤2 (ECOG scale).
8. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of the study.
9. The patient is willing and able to comply with the protocol for the duration of the study, including hospital visits for treatment and scheduled follow-up visits and examinations.
10. Life expectancy of at least 12 weeks.

Exclusion Criteria:

1. Any chemotherapy or radiotherapy (except for palliative reasons) administered four weeks prior to start of study treatment (or a longer period depending on the defined characteristics of the agents used). Patients may continue the use of bisphosphonates for bone disease and corticosteroids provided the dose is stable before and during the study. Heavily pre-treated patients (>2 courses of previous chemotherapy and/or extensive irradiation leading to bone marrow deficiency) will be excluded from the study.
   Bone marrow deficiency is defined as the occurrence of one or other of the events below:
   -treatment delays in previous chemotherapy courses due to bone marrow toxicity.
   -previous chemotherapy courses requiring growth factor support
2. Dose escalation phase
   More than two previous courses of platinum-containing chemotherapy
   Non-randomised dose expansion phase:
   More than two previous courses of platinum-containing chemotherapy, except for metastatic triple negative breast cancer patients who must have had no previous platinum-containing chemotherapy.
   Randomised dose expansion phase:
   Patients where platinum therapy is not indicated
3. Major surgery within 4 weeks of starting the study and patients must have recovered from the effects of major surgery.
4. Patients with an active second primary cancer, except adequately treated basal skin cancer or carcinoma in-situ of the cervix. An active second primary cancer is defined as one with a disease free interval of < 3 years.
5. Pre-existing peripheral neuropathy >grade 1.
6. Any co-existing medical condition that in the investigator's judgment will substantially increase the risk associated with the patient's participation in the study, e.g. co-existing serious active infection requiring parenteral antibiotics, or other serious concurrent illness which, in the opinion of the investigator, precludes participation in the study.
7. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or compliance with the study protocol.
8. Symptomatic brain metastases. A scan to confirm the absence of brain metastases is not required.
9. Gastrointestinal disorders likely to interfere with absorption of the study drug (e.g. partial bowel obstruction or malabsorption).
10. Patients who are unable to swallow oral medication.
11. Patients with a history of allergic reactions to carboplatin, platinum containing compounds or mannitol.
12. Persistent toxicities (grade 2 or greater) from any cause.
13. Pregnant or breast-feeding women.
14. Patients with hepatic disease, e.g. patients with known serologically positive. Hepatitis B or Hepatitis C as they may be more at risk of toxicity from KU-0059436.
15. Immunocompromised patients, e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV).
16. Treatment with any investigational product during the last 30 days.
17. Patients with a known history of severe hypersensitivity reactions to products containing paclitaxel or to any excipient, especially polyoxyethylated castor oil (e.g. Cremophor EL, present in cyclosporine for injection concentrate and teniposide for injection concentrate).
18. Patients requiring treatment with inhibitors or inducers of CYP3A4 (see Section 7.11 for guidelines and wash-out periods).

Restrictions:

1. Contraception
Patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 12 weeks after last dose of study drug(s).

- Condom with spermicide

and one of the following:

- oral contraceptive or hormonal therapy (e.g. hormone implants)

- Placement of an intra-uterine device (see Appendix IV as consideration should be given to the type of device/system used)

Appendix IV provides details of acceptable birth control methods to be used within the study.

Postmenopausal females are defined as:

- Natural menopause with menses >1 year ago
- Radiation-induced oophorectomy with last menses >1 year ago
- Chemotherapy-induced menopause with 1 year interval since last menses
- Serum follicle stimulating hormone, luteinising hormone and plasma oestradiol levels in the postmenopausal range for the institution
- Bilateral oophorectomy or hysterectomy.

Male subjects must use a barrier method of contraception from starting investigational product and for 12 weeks after the last dose.

2. Palliative radiotherapy

Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.

3. Administration of other anti-cancer agents

Patients must not receive any concurrent anti-cancer therapy, including investigational agents, while on-study. Patients may continue the use of bisphosphonates for bone disease and corticosteroids provided the dose is stable before and during the study.

4. Other Concomitant Medication

Caution should be exercised in the concomitant use of amino glycosides with carboplatin, as this may result in increased renal and/or audiologic toxicity.

Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either cytochrome P450 isoenzymes CYP2C8 or CYP3A4 (e.g. erythromycin, fluoxetine, gemfibrozil).

Patients requiring treatment with inhibitors or inducers of CYP3A4 (see Section 7.11 for guidelines and wash-out periods).

Test product, dose and mode of administration, batch no.: KU-0059436 Gelucire® 44/14 (capsule), orally, escalating dose, twice daily or once daily, continuously or discontinuously. KU-0059436 Melt-Extrusion [tablet] formulation twice daily or once daily, continuously or discontinuously.

Duration of treatment: Combination treatment with KU-0059436 and/or carboplatin/paclitaxel may continue for as long as the Investigator feels that the patient is receiving benefit and is free from intolerable toxicity.

A patient may continue on monotherapy KU-0059436 (tablet or capsule) if in the investigator's opinion they are deriving clinical benefit from KU-0059436 treatment and have to stop carboplatin/paclitaxel treatment due to toxicity or because they have completed the prescribed course. If the patient is enrolled in the randomised dose expansion phase the tumour assessment at week 12 must be completed prior to receiving KU-0059436 monotherapy (unless otherwise agreed with AstraZeneca).

At the discretion of the PI and in consultation with AstraZeneca, the patient may receive up to the optimal recommended monotherapy dose, however once a dose is selected patients may not escalate the KU-0059436 again.

Patients in the dose escalation phase and patients in the non-randomised dose expansion phase of the study who have been on study treatment (either KU-0059436 alone or in combination with paclitaxel and/or carboplatin) for over 6 cycles by the time of approval of protocol amendment 6, will have a final study assessment as per the Final Visit schedule (section 9.4). This will be the last data point recorded for each patient for the purpose of the clinical study. Patients, who remain on KU-0059436 alone or KU-0059436 in combination with carboplatin/paclitaxel, after this time point will have assessments in line with the clinical protocol or as defined by local clinical practice.

Patients in the randomised dose expansion phase who have been on treatment for over 6 cycles will continue to be seen by the investigator and have their safety assessments performed in accordance with Table 12. This data will be collected on the clinical database. When the last patient in the randomised dose expansion phase completes a minimum of 12 months of KU-0059436 monotherapy or there are no more patients remaining on treatment in the study, whichever is the earlier, the clinical study database will close to new data.

The investigator will continue to report SAEs to Theradex within 24hrs of becoming aware of the event up to and including 30 days after the patient stops receiving KU-0059436. The overall duration of the study (defined as FSI to last patient stopping treatment) is anticipated to be approximately 8 years.

Reference therapy, dose and mode of administration, batch no.: Carboplatin, target AUC 4 to AUC 6, intravenously, based on a 21 day cycle (Part I). Carboplatin target AUC (to be determined in Part I) and paclitaxel, up to target 175mg/m^2, intravenously over 3 hours, based on 21 day cycle (to be determined in Part IIa). Weekly paclitaxel, 80 mg/m^2, intravenously over 3 hours, based on a 28 day cycle (in parallel with Part IIa).

Part IV Carboplatin, up to a target AUC 6 and paclitaxel, up to a target 175mg/m^2.

KU-0059436 (capsule formulation) 200 mg bid days 1-10 of a 21 day cycle in combination with carboplatin, AUC 4, and paclitaxel, 175mg/m^2 will be the comparator arm in the randomised dose expansion.

Criteria for evaluation: Safety: Safety data, including laboratory parameters and adverse events, will be collected for all patients in order to determine the toxicity, reversibility of toxicity, and dose limiting toxicity of orally administered KU-0059436 when given in combination with i.v. carboplatin and a paclitaxel / carboplatin (TC) doublet and in combination with paclitaxel.

Anti-tumour activity: Although tumour response is not the primary endpoint of this study, patients with measurable disease will be assessed by RECIST criteria.

Pharmacokinetic and pharmacodynamic data will also be collected.

Statistical methods: The study is descriptive in nature and is designed to provide provisional results regarding anti-tumour activity in specific patient populations. The sample size is based on clinical and regulatory considerations and has no formal statistical basis. Descriptive statistics and data listings will be used to describe the study population, the observed anti-neoplastic response and the biologic response. Anti-neoplastic response for the different populations included in the non-randomised and randomised dose expansion phases of the study will be evaluated separately. In the randomised dose expansion phase, anti-neoplastic response will also be evaluated according to treatment arm. All reported symptoms and adverse events will be coded according to the MedRA coding system and presented and summarized by dose. Crude incidence rates will be based on the maximum intensity CTC grade for each patient. All patients who receive any amount of KU-0059436 will be included in these analyses. 95% confidence intervals will be calculated where appropriate.

Pharmacokinetic parameters for KU-0059436 will be calculated using non-compartmental analyses using WinNonLin. The carboplatin and paclitaxel AUC will be calculated based on PK samples taken during the dose escalation phase.

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1.0 INTRODUCTION

1.1 PARP and PARP-1 Inhibition

Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] or PAR polymerisation is a unique post-translational modification of histones and other nuclear proteins that contributes to the survival of proliferating and non proliferating cells following deoxyribonucleic acid (DNA) damage. This event represents an immediate cellular response to DNA damage and involves the modification of glutamate, aspartate and lysine residues with the addition of long chains of Adenosine diphosphate (ADP)-ribose units, derived from Nicotine adenine dinucleotide (NAD)+, onto the DNA-binding proteins. The enzymes that catalyse this process, poly (ADP-ribose) polymerases (PARPs), are critical regulatory components in DNA damage repair and other cellular processes. They now comprise a large and expanding family of 18 proteins, encoded by different genes and displaying a conserved catalytic domain in which PARP-1 (113 kDa), the initial member, and PARP-2 (62 kDa) are so far the sole enzymes whose catalytic activity has been shown to be immediately stimulated by DNA strand breaks. Moreover, many of the identified family members interact with each other, share common partners and common sub-cellular localisations suggesting functional redundancy and possibly fine-tuning in the regulation of post-translational modification of proteins.

The range of biological roles involving PARP proteins is wide. This includes DNA repair and maintenance of genomic integrity, regulation of protein expression at the transcriptional level, regulation of cellular replication and differentiation, regulation of telomerase activity, involvement in cell elimination pathway by necrosis and serving as a signal for protein degradation in oxidatively injured cells (Virag L and Szabo C, 2002).

Of the various members of the PARP enzyme family, only PARP-1 and PARP-2 work as DNA damage sensor and signalling molecules. PARP-1 is a nuclear enzyme consisting of 3 domains, the N-terminal DNA-binding domain containing 2 zinc fingers, the auto-modification domain and the C-terminal catalytic domain. It binds to both single and double-stranded DNA breaks through the zinc-finger domain. PARP-1 catalyses the cleavage of NAD+ into nicotinamide and ADP-ribose, the latter is then synthesised to form branched nucleic acid-like polymers covalently attached to nuclear acceptor proteins. This branched ADP-ribose polymer is highly negatively charged, thereby affecting the function of the target proteins. Histones have been found to be acceptors of poly ADP-ribose, the negative charge leads to electrostatic repulsion between DNA and histones. This has been implicated in chromatin remodelling, DNA repair and transcriptional regulation. Other transcriptional factors and signalling molecules shown to be poly-ADP-ribosylated by PARP-1 are nuclear factor-κB, DNA-dependent protein kinase, p53, topoisomerase-I, lamin B and PARP-1 protein itself (Virag L and Szabo C, 2002).

PARP-1 activation leads to DNA repair through the base excision repair (BER) pathway, and cells deficient in PARP-1 have been shown to have delayed DNA repair function. Like PARP-1, PARP-2 also responds to DNA damage and will similarly lead to single strand DNA repair. For both proteins inactivation and cleavage promotes apoptosis and is part of the apoptotic cascade. Loss of PARP-1 activity in

cells or in knockout mice leads to both radio- and chemo-sensitisation. Moreover, increased PARP-1 activity has been found in many tumour types. The use of PARP inhibitors, like the knockout studies, has confirmed that in combination an enhancement of the antitumour activity of radiation and DNA damaging cytotoxics occurs (Virag L and Szabo C, 2002) and (Nguewa PA, Fuertes MA, Valladares *et al*, 2005).

1.2 Homologous Recombination Deficiency and PARP

The molecular targeting of KU-0059436 to specific subsets of tumours has raised the opportunity for increased therapeutic index in these susceptible tumour populations when using a PARP 1 inhibitor, either as a monotherapy, or with DNA damage inducing chemotherapeutic agents. The Investigational Medicinal Product (IMP) displays anti-tumour activity to a variety of tumour cell lines and this sensitivity of the cells is known in some instances and believed in others to depend upon components of a defective homologous recombination capability. As a major example of this selective activity, the breast cancer (BRCA)-/- gene tumours (both BRCA1 and BRCA2) are seen to be highly sensitive to PARP inhibition. Recent studies indicate that PARP inhibition in BRCA1 and BRCA2 homozygous null cells, but not the isogenic BRCA heterozygous cells, leads to selective cell death. The BRCA1 and 2 genes encode proteins that are implicated in homologous DNA strand break repair, known as homologous recombination. BRCA1 or BRCA2 dysfunction profoundly sensitises cells to PARP inhibition leading to chromosomal instability, cell cycle arrest and cell death (McCabe N *et al*, 2004; Farmer H *et al*, 2005). This sensitivity compared to unaffected heterozygous tissue, provides a large therapeutic window for PARP inhibition.

1.3 Epigenetic Suppression of the Breast Cancer (BRCA) Gene

"BRCAness" is the term given to the phenotype that some sporadic tumours share with familial-BRCA cancers. Epigenetic mechanisms of gene inactivation are well recognised to result in silencing of tumour-suppressor genes. Aberrant methylation of the BRCA1 promoter is found in 11-14% of sporadic breast cancers, primarily in the basaloid "triple negative" (ER-, PR-, HER2-) breast cancers, and in 5-31% of ovarian cancers. This phenotype may also be present in cervical, head and neck and prostate cancers. Identification of the BRCAness phenotype has been reported to portend clinical benefit from drug therapy inducing DNA-damage (Turner N et al, 2004).

Recently, deficiencies in a number of additional components of the homologous recombination repair pathway have also been demonstrated to confer sensitivity to PARP inhibition (McCabe et al, 2006). Moreover, inactivation of a number of these components has been reported in a range of solid tumours. For example, the Fanconi anaemia proteins that are also involved in DNA repair processes, have been shown to be inactivated in lung, oral cancer and cervical cancer cell lines by promoter hypermethylation, rendering these cells highly sensitive to DNA cross-linking agents including platinum-based therapies (Marsit CJ et al, 2004; Narayan G et al, 2004). Recent evidence indicating sensitivity of BRCA1 and BRCA2 deficient cells to PARP inhibition suggests that epigenetic modification of the Fanconi anaemia/BRCA pathway may also lead to activity of PARP inhibitors in these tumour types.

2.0 RELEVANT PRE-CLINICAL RESULTS

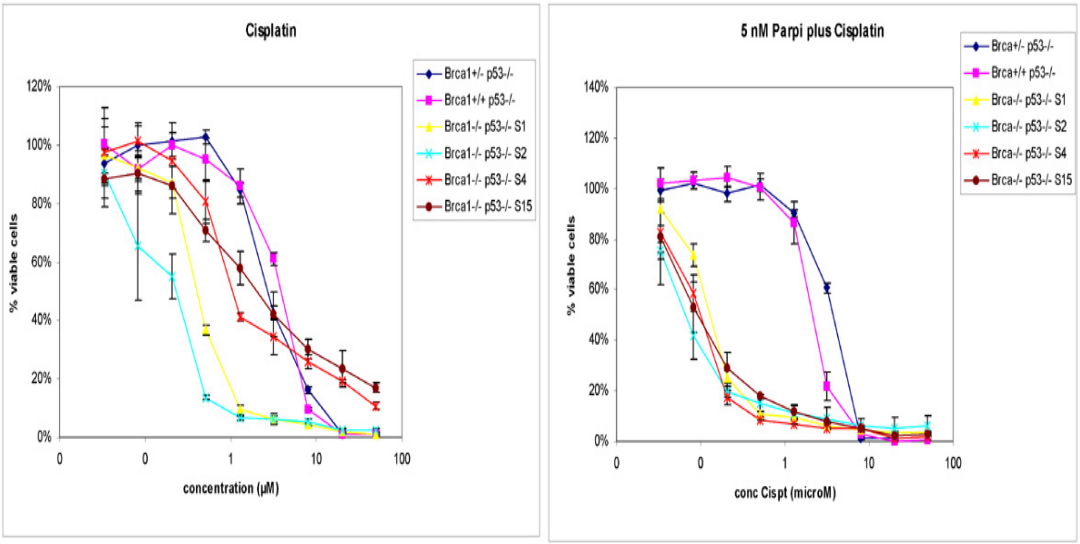
2.1 KU-0059436

KU-0059436 is a potent inhibitor of PARP-1. KU-0059436 shows significant monotherapy activity in tumour cells with defective components of homologous recombination, which includes cells with the BRCA1 -/- and BRCA2 -/- genotype. Inhibition of PARP activity using KU-0059436 also sensitises cells to the cytotoxic effects of ionising radiation and certain chemotherapies, notably camptothecins and alkylating agents like DTIC and temozolomide.

2.2 Experimental Animal Models of BRCA Deficiency

In transgenic mouse knockout models, where the BRCA1 protein has been lost, mice spontaneously develop mammary tumours that are characteristically similar to humans. These tumours take several months to develop but once established become very aggressive and are histopathologically similar to human breast tumours deficient in BRCA1. Both the syngeneic tumours and the cell lines that can be derived from them can be tested for their sensitivity to PARP inhibitors and/or cross-linking agents such as cisplatin and carboplatin. The testing of the PARP inhibitor KU-0059436 in cells derived from spontaneous BRCA-1 tumours significantly enhances the activity of platinum treatment (see Figure 1 below).

Figure 1: Efficacy of PARP Inhibitor plus cisplatin versus cisplatin alone in the Kcre; BRCA1/$^{2flox/flox}$; p53$^{flox/flox}$ Mouse Model



S1, S2, S4 and S15 are four BRCA1-deficient cell lines generated from four independent spontaneous tumours.
Sensitivity of homozygous BRCA-1 deficient cells to cisplatin compared to those BRCA1 heterozygous or BRCA1 wild type is enhanced by the addition of PARP inhibitor at 5nM concentration.

2.3 Summary of Preclinical Pharmacokinetics

Pharmacokinetics (PK) data for the rat showed sex differences in absorption parameters for individual studies, however these observations were variable and, as no gender difference in PK parameters was seen in the dog, it seems unlikely that these are of relevance to the proposed clinical study. Higher systemic exposure in female rats compared to males at the same dose level accounts for their apparently greater sensitivity to the drug, as seen by haematological and histological changes in the toxicology studies. In the dog, toxicokinetics were similar for males and females.

Distribution of KU-0059436 is typical for an orally administered foreign compound, in the gastro-intestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. Metabolism data to date are limited and further investigations are ongoing. To date, several metabolites have been observed in pre-clinical studies, although their identification and activity have not been confirmed as yet. Similar metabolite profiles were observed in the urine and faeces of male and female rats. Excretion is primarily via the faeces and to a lesser extent via the urine; in a study of [14C]-KU-0059436 in the rat, excretion was 76±13% (in faeces) and 20±11% (in urine).

2.4 Summary of Toxicological Data

KU-0059436 has shown comparatively low toxicity, other than myelotoxicity, in toxicological testing in a standard range of safety pharmacology studies, i.e. dog cardiovascular and respiratory function tests, and the rat Irwin test.

The toxicology studies indicate that the target organ of toxicity is the bone marrow. Specific ex vivo work has been conducted exposing human bone marrow cells to KU-0059436, which has confirmed that KU-0059436 is also active against human marrow. However, the cytotoxic effect becomes evident at a higher concentration than that which fully ablates PARP activity (mean IC50 of 2.7 μM for myelosuppression [n = 4 human donors] compared with 0.1 μM for total PARP-1 activity inhibition). These data, along with the 28-day dog and rat studies, show a myelotoxic effect that is mild-to-moderate and is reversible. Platelets appear first affected, followed by white blood cells. Twenty-six week (26-week) repeat oral dose studies of KU-0059436 in rat and dog have given similar results, with the drug being well tolerated and no drug related mortality. Importantly, oncology clinics are well used to monitoring for the onset of such effects and are expert in their management.

KU-0059436 showed no mutagenic potential in the Ames test, was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test, and was genotoxic in the rat micronucleus test; these findings are not uncommon for many therapeutic agents used in oncology, and so do not present an unacceptable risk when appropriately clinically managed.

2.5 New Melt-Extrusion (Tablet) Formulation: Pre-clinical experience

The current Gelucire® 44/14 (capsule) formulation of KU-0059436 is a large capsule (size zero) containing 50 mg of KU-0059436. The proposed formulation of micronised KU-0059436 in capsules containing Gelucire® has an oral bioavailability of greater than 85% in the dog. Two capsules strengths (red 10 mg and white 50 mg capsules) are available.

Dose finding studies are on going however; currently the clinical efficacious dose is projected to be between 200 mg and 400 mg bid. This will result in a daily dose between 8 and 16 large capsules. Attempts to increase the drug loading of this capsule and maintain similar exposure in pre clinical models have been unsuccessful. Therefore, an extensive formulation exercise has been undertaken to find a formulation with improved drug loading and bioavailability.

These formulation efforts have been focussed on improving the exposure of KU-0059436 and after comparing potential drug delivery approaches, a formulation which renders the KU-0059436 amorphous and presents the drug in a solid dispersion in copovidone (30% drug loading) was developed using a melt extrusion process. The milled extrudate is then blended with pharmacopoeial excipients and compressed into a tablet. The tablets are then film coated.

The melt-extrusion [tablet] formulation has completed investigations in the PK phase of AstraZeneca study D0810C00024 (EudraCT number: 2008-003697-18). The single dose plasma concentration-time data obtained has been subjected to pharmacokinetic modelling followed by multiple dose simulation to predict likely exposures following multiple (bid) dosing of the tablet formulation. This work predicts that tablet doses of between 120 and 205mg bid would be expected to deliver exposures, in at least 95% of patients dosed, which would be within both the C_{max} and $AUC_{0-\tau}$ ranges previously seen following both the 200 and the 400 mg bd capsule dose.

It is expected that the new Melt-Extrusion (tablet) formulation of KU-0059436 should provide a more bioavailable and patient friendly formulation by minimising the number of dosage units.

2.6 Overall Pre-clinical Summary

KU-0059436 is a potent inhibitor of PARP-1 which shows significant activity in tumour cells deficient in BRCA1 and BRCA2 genotypes and against tumour models or BRCA deficiency. KU-0059436 has shown comparatively low toxicity in toxicological testing, and is therefore perceived as a potential means of obtaining therapeutic advantage by directly inhibiting PARP-1 and hence tumour growth, either when used as a ‘stand-alone’ treatment or in combination therapy with other cytotoxic agents (such as alkylating agents and the tecans).

3.0 SUMMARY OF CLINICAL EXPERIENCE

A single Phase I, ascending dose, safety and tolerability study of KU-0059436 in

patients with solid tumours is being conducted at two centres (United Kingdom and the Netherlands EudraCT No. 2005-001435-29).

Myelosuppression is a predicted dose-limiting toxicity from the pre-clinical animal toxicology studies. Study KU36-92 has enrolled patients with advanced cancer, many of whom have received prior chemotherapy. This patient population is known to experience myelosuppressive effects as a result of both their underlying condition (which may include bone marrow infiltration), and chemotherapy (Warrell et al, 2004).

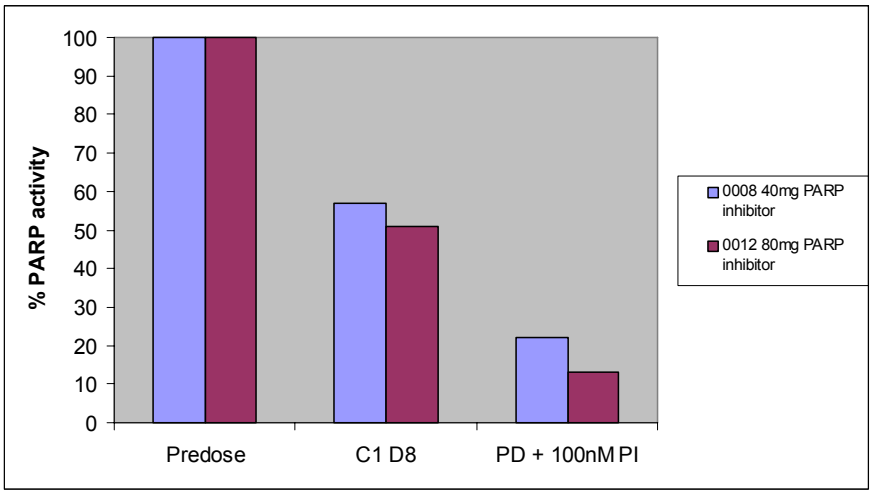
Of 3 patients treated with KU-0059436 at 600 mg b.d., 2 experienced events that were defined as Dose-Limiting Toxicity. The first patient with mesothelioma experienced CTC grade 4 thrombocytopenia, without any evidence of bleeding. The second patient with breast cancer experienced CTC grade 3 somnolence. As per the protocol, the maximum tolerated dose was defined in this study as 400 mg b.d.

KU-0059436 appears to be generally well tolerated in patients with various solid tumours at doses up to and including 600 mg twice daily, as monotherapy. The emerging safety profile observed for KU-00059436 supports further studies in cancer patients.

Two patients (pleural sarcoma and adrenal carcinoma) dosed at 10 mg/day and 40 mg/day respectively, achieved stable disease (SD) for 6 months. A third patient (100 mg b.d.), with a strong family history suggestive of BRCA impairment, who had relapsed within 4 months of a platinum-based therapy, had a confirmed partial response (PR) after three cycles of KU-0059436 and a cancer antigen (CA)-125 decrement of >80%. The patient showed a prolonged response (partial response) for 8 cycles of KU-0059436 treatment. Further unconfirmed evidence of anti-tumour activity was seen in additional BRCA patients at 200mg and 400 mg b.d.

Pharmacodynamically, the study has demonstrated significant tumour PARP-1 inhibition at doses of 40 mg once daily and above when dosed on days 1-14 of a 21-day cycle.

Figure 2: PD: Tumour samples for PARPI inhibition



50% PARP Inhibition was seen in tumour biopsies in two patients, 0008 and 0012 (EudraCT No. 2005-001435-29).

The observation of concentration-dependent pharmacodynamic activity (decreased PAR activity in peripheral blood mononuclear cells [PBMC]) confirms pharmacological activity at a well tolerated dose and provides an initial indication of the biological activity within the tolerated dose range. This level of PARP inhibition is of the same magnitude as that observed with the PARP inhibitor AG014699 where potentiation of both anti-tumour activity and myelotoxicity was observed (Plummer R, et al, 2006).

Therefore clinical study data to date in patients with advanced cancer have shown KU-0059436 to be well tolerated with mainly mild to moderate (CTC grade ≤2) toxicities. In addition, consistent with existing pre-clinical data, preliminary indication of single agent activity has been observed in BRCA patients. Please refer to the current Investigator's Brochure for a complete review of the safety and efficacy of the product.

3.1 Rationale for the Study

The phase I study has illustrated that KU-0059436 can effectively inhibit the PARP enzyme. Inhibition of PARP affects the repair of DNA damage. Whilst the ability to repair DNA is desirable in most cases, in cancer therapy it may enable tumour cells to recover from chemotherapy thus preventing effective treatment.

The potential to effectively inhibit the DNA repair in tumour cells following cytotoxic agents may potentiate the effects of chemotherapy and lead to better responses in some tumours. This concept is supported by the preclinical studies.

A related clinical study of Dacarbazine (DTIC), a pro-drug to 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC), in combination with KU-0059436 patients with advanced solid tumours (EudraCT No. 2006-003826-26) has received regulatory approval and is ongoing.

Carboplatin

Carboplatin exerts its cytotoxic and therapeutic effect primarily by forming intrastrand and DNA adducts with adjacent guaninine residues in tumour cell DNA, thereby inhibiting tumour growth (Schurig JE, Rose WC, Catino JJ, et al). Since the platins were introduced they have been widely used for the treatment of many cancers particularly lung, ovary, head and neck, bladder and germ cell cancers.

Although previously platins were not extensively used in breast cancer, the use of such treatment is now being revisited, both in early disease studies (Slamon and Pegram, 2001; Crown JP, 2001), neoadjuvant (Garber et al, 2006) and in advanced disease with triple negative patients, where BRCA abnormalities and HR defects are known to be more prevalent. It is known that PARP inhibition can selectively kill cells with homologous recombination defects: therefore the combination of carboplatin with KU-0059436 may be an effective anti-cancer combination and warrants further investigation.

Paclitaxel and Carboplatin

The paclitaxel/carboplatin doublet is standard treatment for advanced ovarian cancer. It has also been found to give a high response rate in patients with metastatic /recurrent triple negative breast cancer, including patients with prior exposure to taxanes and those with large volume disease. It is therefore expected that the addition of paclitaxel to the KU-0059436 and carboplatin administration will lead to the best possible clinical outcome for these patients, once the appropriate dose and dose administration schedule of all three drugs in combination is established.

In order to maximise the effect of the combination on the tumour, it is considered important to maintain the PARP inhibition and therefore KU-0059436 will be dosed continuously in the first instance, and if this combination is not tolerated, discontinuous dosing may be tested. Carboplatin, and the combination of carboplatin and paclitaxel will be administered using a 3-week cycle according to long-standing clinical practice.

Paclitaxel

Determination of the safety profile of two different doses of KU-0059436 and paclitaxel in combination, may provide useful information on the mechanism of the thrombocytopenia noted in this study. The thrombocytopenia noted in previous cohorts could be the synergistic effect of the carboplatin + KU-0059436 combination, or a primary effect of KU-0059436 on the ability of bone marrow to recover after carboplatin administration. Given that paclitaxel has been shown to be protective with respect to platelet formation in combination with platinum agents, if thrombocytopenia is noted in patients receiving a paclitaxel + KU-0059436 combination, it is more likely to be a primary effect of KU-0059436. Furthermore, understanding the safety profile of KU-0059436 + paclitaxel alone, may provide information to support decisions in parts II and III of the study.

4.0 STUDY OBJECTIVES

4.1 Primary objective

To investigate the safety and tolerability and establish;

- Either the dose of KU-0059436 which can be safely administered and which causes inhibition of PARP in combination with an active dose of a paclitaxel / carboplatin (TC) doublet.
- Or the maximum tolerated dose (MTD) of KU-0059436 in combination with a paclitaxel / carboplatin (TC) doublet.

4.2 Secondary objectives

- To identify the Dose Limiting Toxicity (DLT) of the combination of KU-0059436 and a paclitaxel / carboplatin (TC) doublet.
- To determine the plasma pharmacokinetic profile of:
  - KU-0059436 alone
  - KU-0059436 in combination with carboplatin
  - KU-0059436 in combination with a paclitaxel / carboplatin (TC) doublet
  - KU-0059436 in combination with paclitaxel.
- Randomised Dose Expansion Phase Only: To investigate the effect of food (pre-dose standard meal) on the pharmacokinetics (PK) of oral KU-0059436.
- To investigate the pharmacodynamic profile over time in surrogate tissue of KU-0059436 when given in combination with a paclitaxel / carboplatin (TC) doublet.
- To enable a preliminary assessment, in specific patient populations, of the safety and tolerability and anti-tumour activity of up to two dose combinations of KU-0059436 tablet formulation in combination with a paclitaxel / carboplatin (TC) doublet versus KU-0059436 (capsule formulation) at 200 mg bid days1-10 of a 21 day cycle in combination with AUC 4 carboplatin and paclitaxel (175mg/m^2). (Randomised Dose Expansion phase).
- To determine the safety profile of KU-0059436 in combination with paclitaxel given at two dose levels.
- To determine the safety and tolerability profile of the KU-0059436 Melt-Extrusion [tablet] formulation in combination with a paclitaxel/carboplatin (TC) doublet.

4.3 Exploratory objective

To investigate exploratory biomarkers in whole blood, serum, urine and tumour biopsies (on-treatment and historical) to ascertain if there are any which differentiate treatment effects, and to investigate their correlation with disease progression/response to therapy or an improved understanding of disease.

5.0 STUDY POPULATION

Male or female patients with histologically or cytologically diagnosed malignant solid tumours will be recruited to the dose escalation phase of the study; these patients must

have had no more than 2 previous platinum based chemotherapy regimens.
In the dose escalation phase of the study up to approximately 180 patients will be enrolled in the carboplatin and carboplatin / paclitaxel (TC) doublet arms.

Additionally, up to 12 evaluable patients will be enrolled in a comparator and parallel KU-0059436 + weekly paclitaxel dose escalation arm.

Additionally 15 female patients with histologically or cytologically confirmed platinum naïve metastatic triple negative breast cancer and female patients with advanced ovarian cancer will be enrolled into a non-randomised dose expansion of a selected KU-0059436 / carboplatin / paclitaxel combination dose. Breast cancer patients must have had no previous platinum based chemotherapy.

Other doses in the dose escalation phase deemed to be tolerated can be expanded in the non-randomised dose expansion to further assess tolerability. Up to 30 patients in total can be included in these expansions.

A randomised expansion may be implemented to compare up to two selected KU-0059463 (tablet formulation) / carboplatin / paclitaxel dose combination arms versus KU-0059436 (capsule formulation) at 200 mg bid days1-10 of a 21 day cycle in combination with AUC 4 carboplatin and paclitaxel (175mg/m^2).

Approximately 45 female patients with histologically or cytologically confirmed measurable metastatic breast cancer and female patients with measurable advanced ovarian cancer, where further treatment with platinum based chemotherapy is indicated, may be enrolled in the randomised dose expansion phase of the study (~15 patients per arm). This sample size was based on obtaining a sufficient number of patients for comparisons of safety and tolerability between the treatment arms, whilst exposing as few patients as possible to study procedures.

In addition, this number of patients with measurable disease will provide sufficient power to allow a preliminary comparison of anti-tumour activity between the selected KU-0059463 tablet formulations and the 200 mg bid capsule formulation (days 1-10) in combination with carboplatin and paclitaxel.

As a measure of study precision, if there is truly no difference between formulations in mean percentage change in tumour size then there will be 79% power to rule out a difference of 20% (assuming a significance level of 20% 1-sided, and standard deviation of 33%).

6.0 INCLUSION AND EXCLUSION CRITERIA

6.1 Inclusion Criteria

1. Full-informed written consent.
2. Dose escalation phase:
   Male or female patients with a histologically or cytologically diagnosed malignant solid tumour.
   Non-randomised dose expansion phase:
   Female patients with histologically or cytologically diagnosed metastatic

triple-negative breast cancer (platinum naïve) and female patients with histologically or cytologically diagnosed advanced ovarian cancer, where further treatment with platinum based chemotherapy is indicated.
Randomised dose expansion phase:
Female patients with histologically or cytologically diagnosed measurable metastatic breast cancer and female patients with histologically or cytologically diagnosed measurable advanced ovarian cancer, where further treatment with platinum based chemotherapy is indicated

3. **Randomised Dose Expansion Phase Only**: One or more measurable lesions, at least 10 mm in the longest diameter (LD) by spiral CT scan, or 20 mm with conventional techniques, according to RECIST criteria, not irradiated within 12 weeks of the first administration of study drug.
4. Adequate bone marrow, hepatic and renal function including the following:
    a. Haemoglobin ≥10.0 g/dl (6.2mM), absolute neutrophil count ≥1500 x 10^6/L, platelets ≥100,000 x 10^6/L;
    b. Total bilirubin : ≤1.25 x upper normal limit;
    c. AST (SGOT), ALT (SGPT) : ≤2.5 x upper normal limit;
    d. Creatinine: ≤1.5 x upper normal limit.
5. Creatinine clearance (Jaffe or enzymatic serum creatinine) within normal range (>60ml/min).
6. Age ≥18 years.
7. Performance status (PS): ≤2 (ECOG scale).
8. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of the study.
9. The patient is willing and able to comply with the protocol for the duration of the study, including hospital visits for treatment and scheduled follow-up visits and examinations.
10. Life expectancy of at least 12 weeks.

6.2 Exclusion Criteria

1. Any chemotherapy or radiotherapy (except for palliative reasons), administered within four weeks prior to start of study treatment (or a longer period depending on the defined characteristics of the agents used). Patients may continue the use of bisphosphonates for bone disease and corticosteroids provided the dose is stable before and during the study. Heavily pre-treated patients (>2 courses of previous chemotherapy and/or extensive irradiation leading to bone marrow deficiency) will be excluded from the study.
   Bone marrow deficiency is defined as the occurrence of one or other of the events below:
   -treatment delays in previous chemotherapy courses due to bone marrow toxicity.
   -previous chemotherapy courses requiring growth factor support.
2. Dose escalation phase:
   More than two previous courses of platinum-containing chemotherapy.
   Non-randomised dose expansion phase:
   More than two previous courses of platinum-containing chemotherapy, except for metastatic triple negative breast cancer patients who must have had no previous platinum-containing chemotherapy.

Randomised dose expansion phase
Patients where platinum therapy is not indicated

4. Major surgery within 4 weeks of starting the study and patients must have recovered from the effects of major surgery
5. Patients with an active second primary cancer, except adequately treated basal skin cancer or carcinoma in-situ of the cervix. An active second primary cancer is defined as one with a disease free interval of < 3 years.
6. Pre-existing peripheral neuropathy >grade 1.
7. Any co-existing medical condition that in the investigator's judgement will substantially increase the risk associated with the patient's participation in the study, e.g. co-existing serious active infection requiring parenteral antibiotics, or other serious concurrent illness which, in the opinion of the investigator, precludes participation in the study.
8. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or compliance with the study protocol.
9. Symptomatic brain metastases. A scan to confirm the absence of brain metastases is not required.
10. Gastrointestinal disorders likely to interfere with absorption of the study drug (e.g. partial bowel obstruction or malabsorption).
11. Patients who are unable to swallow oral medication.
12. Patients with a history of allergic reactions to carboplatin, platinum containing compounds or mannitol.
13. Persistent toxicities (grade 2 or greater) from any cause.
14. Pregnant or breast-feeding women.
15. Patients with hepatic disease, e.g. patients with known serologically positive. Hepatitis B or Hepatitis C as they may be more at risk of toxicity from KU-0059436.
16. Immunocompromised patients, e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV).
17. Treatment with any investigational product during the last 30 days.
18. Patients with a known history of severe hypersensitivity reactions to paclitaxel and products containing polyoxyethylated castor oil e.g. Cremophor EL (present in cyclosporine for injection concentrate and teniposide for injection concentrate) (Cancer Treatment, 4th ed. W.B. Saunders Company).
19. Patients requiring treatment with inhibitors or inducers of CYP3A4 (see Section 7.11 for guidelines and wash-out periods).

6.3 Restrictions/Precautions

6.3.1 Contraception

Patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 3 months after last dose of study drug(s).

- Condom with spermicide

and one of the following

- oral contraceptive or hormonal therapy (e.g. hormone implants)

- Placement of an intra-uterine device (see Appendix IV as consideration should be given to the type of device/system used)

Appendix IV provides details of acceptable birth control methods to be used within the study.

Postmenopausal females are defined as:

- Natural menopause with menses >1 year ago
- Radiation-induced oophorectomy with last menses >1 year ago
- Chemotherapy-induced menopause with 1 year interval since last menses
- Serum follicle stimulating hormone, luteinising hormone and plasma oestradiol levels in the postmenopausal range for the institution

1. Bilateral oophorectomy or hysterectomy.

Male subjects must use a barrier method of contraception from starting investigational product and for 12 weeks after the last dose.

6.3.2 Palliative radiotherapy

Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.

6.3.3 Administration of other anti-cancer agents

Patients must not receive any concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates for bone disease and corticosteroids provided the dose is stable before and during the study.

6.3.4 Other Concomitant Medication

For more complete information please see Section 7.11.

Paclitaxel should be used with caution with medicines known to inhibit or induce cytochrome P450 isoenzymes CYP2C8 and CYP3A4.

Caution should be exercised in the concomitant use of amino glycosides with carboplatin, as this may result in increased renal and/or audiologic toxicity.

In vitro data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of KU-0059436 is CYP3A4 and consequently potent inhibitors and inducers of CYP3A4 must not be used during this study for any patient receiving KU-0059436.

7.0 INVESTIGATIONAL PLAN

7.1 Study Design

This is an open-label multi-centre, phase I study of KU-0059436 administered orally

in combination with carboplatin alone and in combination with a paclitaxel / carboplatin (TC) doublet and in combination with paclitaxel alone.

The study consists of a maximum of 4 dose escalation phases to establish first, (Part I), the appropriate dose of KU-0059436 and carboplatin given in combination and thereafter (Part IIa) the appropriate dose of the KU-0059436 and paclitaxel / carboplatin (TC) doublet. Part III of the study, with KU-0059436 administered discontinuously, will only be initiated if a clinically acceptable combination cannot be achieved in Part IIa. Part IIb will determine the safety profile of KU-0059436 and paclitaxel and may determine some of the mechanisms of the bone marrow toxicity, especially thrombocytopenia noted in earlier cohorts, and will be run in parallel (as a comparison) with Part IIa (there is no planned expansion phase following Part IIb).

The dose escalation part of the study will allow recruitment of male and female patients with any malignant solid tumour.

Parts I and IIa of the study will adopt a 3-week schedule for administration for carboplatin and the paclitaxel / carboplatin (TC) doublet in combination with continuously administered KU-0059436.

In Part IIb, paclitaxel will be administered weekly for 3 weeks in a 4-week cycle in combination with continuously administered KU-0059436.

In Part III, a discontinuous dose of KU-0059436 will be administered with the paclitaxel / carboplatin (TC) doublet using a 3-week schedule day 1 to day 10 inclusive, but not from day 11 to day 21.

Other discontinuous KU-0059436 schedules consisting of KU-0059436 administered for pre-defined numbers of days, up to 20 days, within each treatment cycle may also be explored.

In addition to discontinuous KU-0059436 administration, conservative escalations of carboplatin or KU-0059436 may occur. Paclitaxel will remain at 175mg/m2.

Additional cohorts of 3-6 patients will be recruited to Part III of the study to determine the tolerability of a defined Melt-Extrusion [tablet] formulation dose of KU-0059436 in conjunction with paclitaxel/carboplatin (TC). The initial KU-0059436 Melt-Extrusion [tablet] formulation dose to be delivered will be 200mg bid, assuming 200mg bid or above KU-0059436 Gelucire® 44/14 (capsule) has been determined to be tolerable in a previous cohort, similarly the doses of paclitaxel/carboplatin will both be at the same previously tolerated doses.

If upon assessment of the first expansion cohort, it is determined by the investigator and AstraZeneca that from a tolerability point of view this dose/schedule is not appropriate for phase II/III studies, then Part IV of the study will be opened to enable selection of alternate dose/schedules. In Part IV other discontinuous KU-0059436 schedules consisting of KU-0059436 (capsule or tablet) administered for any pre-defined numbers of days, up to 20 days, within each or specified treatment cycle may also be explored. These cohorts may be recruited in parallel upon agreement of AstraZeneca and the investigators

At each new cohort, the duration and timing of the dosing will be decided upon review of the safety, tolerability and operational feasibility of the regimen adopted in previous cohorts, by the investigators and AstraZeneca.

Up to three dose(s) and schedule(s) of the KU-0059436 and paclitaxel / carboplatin (TC) doublet that can be safely administered in the escalation phase may be used for dose expansion and will further establish the safety and tolerability of the KU-0059436 / paclitaxel / carboplatin (TC) doublet dose. The non-randomised expansion phase will only recruit female patients with metastatic triple negative breast cancer and patients with advanced ovarian cancer.

The non-randomised dose expansion phase of the study will only be initiated after review of the safety, tolerability and operational feasibility of the regimen by AstraZeneca and the Investigators.

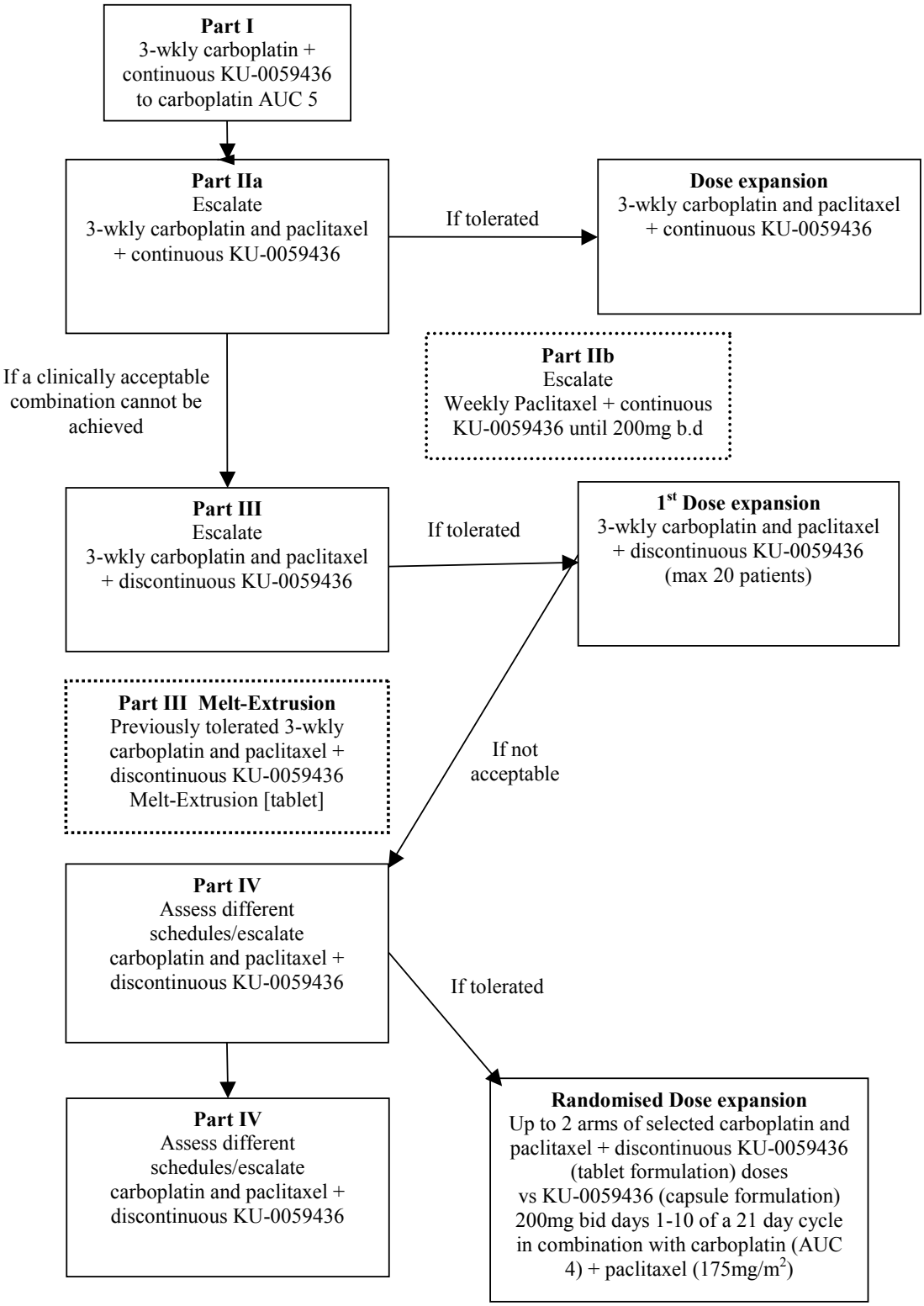
These expansion cohorts may be recruited in parallel upon agreement of AstraZeneca and the Investigators.

Up to two tolerable dose schedules selected from the dose escalation part IV of the study may be explored in a randomised expansion versus KU-0059436 (capsule formulation) at 200 mg bid days 1-10 of a 21 day cycle in combination with AUC 4 carboplatin and paclitaxel (175mg/m^2).

Approximately 45 patients will be recruited in this expansion (~15 patients per arm). The randomised dose expansion phase will only recruit female patients with metastatic breast cancer and patients with advanced ovarian cancer, where further treatment with platinum based chemotherapy is indicated.

The randomised dose expansion phase of the study will only be initiated after review of the safety, tolerability and operational feasibility of the regimen(s) by AstraZeneca and the Investigators.

The study design is summarised as follows:



7.1.1 Dose escalation phase

Part I: KU-0059436 + a 3-weekly schedule of carboplatin.

Parts IIa / III: KU-0059436 + a 3-weekly schedule of paclitaxel / carboplatin (TC)

doublet.

Part IIa will start once a safely administered dose combination or the MTD is established in Part I.

Part III will only be initiated if a clinically acceptable schedule cannot be achieved in Part IIa

Part IV will only be opened if the 1st expansion dose is not appropriate for phase II/III studies.

Part IIb: KU-0059436 + paclitaxel administered on day 8, 15 and 22 of cycle 1 (5 weeks) and on days 1, 8 and 15 of each subsequent 4-weekly cycle. This part will be conducted in parallel with Part IIa or III.

Part I: KU-0059436 + a 3-weekly schedule of carboplatin

In all cycles, KU-0059436 will be administered orally twice daily continuously, in combination with carboplatin through escalating doses.

Cycle 1 will be of 28 days duration and all subsequent cycles will be 21 days duration. In cycle 1, KU-0059436 will be administered twice daily for the first 7 days to allow samples to be taken for KU-0059436 pharmacokinetics.

In cycle 1, carboplatin will be administered once on day 8 of a 28 day cycle. Carboplatin pharmacokinetic (PK) samples will be taken on days 8, 9 and 10 to assess the carboplatin dose as measured by area under the curve (AUC). All subsequent cycles will be of 21 days duration with carboplatin being administered on day 1 at least 1 hour after the patient has taken their KU-0059436 capsules.

The PK sampling timelines are detailed in Section 10.1 of the protocol and in the Biological Sample Handling plan.

Part IIa: KU-0059436 + a 3-weekly schedule of paclitaxel / carboplatin (TC) doublet.

Once the maximum dose of carboplatin that can be administered safely in combination with KU-0059436 has been identified in Part I, paclitaxel will be added to this dose combination, with the objective of increasing the dose of carboplatin to an effective dose of AUC 5 or 6. Initially a dose of paclitaxel used on a 3-weekly basis (90mg/m^2) will be added and if tolerated, the paclitaxel dose will be increased to 135mg/m^2 paclitaxel and finally, to the standard 3-weekly dose of 175mg/m^2 paclitaxel. If AUC 5 cannot be safely administered in the dose escalation phase, intermediate doses of KU-0059436 or paclitaxel may be administered with carboplatin in order to obtain a safe combination with carboplatin AUC 5 or 6 through subsequent dose escalations.

In all cycles, KU-0059436 will be administered orally twice daily continuously, however if 50mg b.d. is not tolerated then 50mg o.d. doses may be tested in a dose escalating scheme.

Cycle 1 will be of 28 days duration and all subsequent cycles will be 21 days duration. In cycle 1, KU-0059436 will be administered twice daily for the first 7 days to allow samples to be taken for KU-0059436 pharmacokinetics.

In cycle 1, paclitaxel followed by carboplatin will be administered once on day 8. Carboplatin pharmacokinetic (PK) samples will be taken on days 8, 9 and 10 to assess the carboplatin dose as measured by area under the curve (AUC). Paclitaxel pharmacokinetic (PK) samples will be taken on days 8 and 9 to assess the paclitaxel dose as measured by area under the curve (AUC).

All subsequent cycles will be of 21 days duration with paclitaxel being administered on day 1 at least 1 hour after the patient has taken their KU-0059436 capsules and carboplatin administered after the completion of a 3 hour paclitaxel infusion.

If a carboplatin dose of AUC 5 can be achieved, the maximum dose of carboplatin, KU-0059436 and paclitaxel safely administered in this part of the study will be used in the dose expansion phase of the study: if not Part III will be initiated.

Patients will be dosed for up to 6 cycles. At the discretion of the investigator patients can receive more than 6 cycles if they have at least stable disease.

Part IIb: KU-0059436 + paclitaxel

In all cycles, KU-0059436 will be administered orally twice daily continuously, in combination with a fixed dose of paclitaxel.

Cycle 1 will be of 35 days duration and all subsequent cycles will be 28 days duration. In cycle 1, KU-0059436 will be administered twice daily alone for the first 7 days to allow samples to be taken for KU-0059436 pharmacokinetics.

In cycle 1, paclitaxel will be administered once on days 8, 15 and 22 of a 35 day cycle. Paclitaxel pharmacokinetic (PK) samples will be taken on days 8 and 9 to assess the paclitaxel PK as measured by area under the curve (AUC). All subsequent cycles will be of 28 days duration with paclitaxel being administered on days 1, 8 and 15 at least 1 hour after the patient has taken their KU-0059436 capsules.

Patients will be dosed for up to 6 cycles. At the discretion of the investigator, patients can receive more than 6 cycles if they have at least stable disease.

The PK sampling timelines are detailed in Section 10.1 of the protocol and in the Biological Sample Handling plan.

Part III: Discontinuous dose of KU-0059436 + paclitaxel / carboplatin (TC) doublet

This part of the study will only be initiated if a clinically acceptable dose cannot be achieved in Part IIa. Each cycle will be 21 days long.

Initially, a discontinuous dose of KU-0059436 will be administered from day 1 to day 10 inclusive, but not from day 11 to day 21. The carboplatin dose will be AUC 4 and paclitaxel 175 mg/m^2.

Thereafter, other dosing schedules for KU-0059436 may be tested with durations ranging from 1-20 days with defined rest periods. In addition within Part III escalations or de-escalations of carboplatin or KU-0059436 may occur to determine

the most effective dose. However, the dose of KU-0059436 will not go below 50mg o.d. or above 400mg b.d., the dose of carboplatin will not be reduced below AUC 4 or increased above AUC 6 and the dose of paclitaxel will not be lower than 90 mg/m2 or higher than 175 mg/m^2.

Additional cohorts of 3-6 patients will be recruited to Part III of the study to determine the tolerability of a defined Melt-Extrusion [tablet] formulation dose of KU-0059436 in conjunction with paclitaxel/carboplatin (TC). The initial KU-0059436 Melt-Extrusion [tablet] formulation dose to be delivered will be 200mg bid, assuming 200mg bid or above KU-0059436 Gelucire® 44/14 (capsule) has been determined to be tolerable in a previous cohort, similarly the doses of paclitaxel/carboplatin will both be at the same previously tolerated doses. As long as the combination doses have been tolerated before in previous cohorts, this cohort may recruit in parallel to other ongoing cohorts.

Lower doses of the Melt-Extrusion tablet or different (previously tolerated) doses of carboplatin/paclitaxel may be tested dependant on emerging safety data, with the possibility of additional cohorts testing these doses if required.

Part IV: Assessment of other discontinuous dose/schedules of KU-0059436 + paclitaxel / carboplatin (TC) doublet

If upon assessment of the first expansion cohort, it is determined by the investigators and AstraZeneca that from a tolerability point of view this dose/schedule is not appropriate for phase II/III studies, then part IV of the study will be opened to enable selection of an alternate dose/schedule. In Part IV other discontinuous KU-0059436 schedules consisting of KU-0059436 (capsule or tablet) administered for any pre-defined numbers of days, up to 20 days, within each or specified treatment cycle maybe explored with carboplatin and paclitaxel. These cohorts may be recruited in parallel upon agreement of AstraZeneca and the investigators.

The alternate schedules to be tested may include offsetting the start dose of KU-0059436 to day 2 or later, to avoid dosing KU-0059436 at the Cmax of carboplatin, which may reduce toxicity. Other schedules that may be tested are alternating cycles of chemotherapy alone dosing and chemotherapy + KU-0059436, which may enable recovery from the toxicity due to the possible potentiating effect of KU-0059436 on carboplatin.

In addition within Part IV escalations or de-escalations of carboplatin or KU-0059436 may occur to determine the most effective dose. However, the dose of KU-0059436 will not go below 50mg o.d. or above 400mg b.d., the dose of carboplatin will not be increased above AUC 6 and the dose of paclitaxel will not be higher than 175 mg/m^2. Carboplatin and paclitaxel will be administered either on a 21 day or weekly schedule.

The duration and timing of the KU-0059436 dosing will be determined by careful review of the safety data from previous cohorts.

Maximum Tolerated Dose

For all drug combinations in Part I, Part IIa, Part IIb, Part III and Part IV of the dose escalation phase, the Maximum Tolerated Dose (MTD) is defined as the prior or

intermediate dose level below the drug-combination that causes Dose-Limiting Toxicity (DLT), in at least 2 patients in a cohort of at least 3 patients. If toxicity is equivocal and it is not possible to determine a DLT with certainty, further cohorts of three patients will be recruited to allow an informed decision to be taken about further dose escalations.

7.1.2 Non-randomised dose expansion phase

KU-0059436 and paclitaxel / carboplatin (TC) doublet

The key objective of the dose expansions is to further determine the safety and tolerability of the established dose from the dose escalation phase in specific patient populations.

It is expected that the MTD will be selected for dose expansion. However, doses of KU-0059436 (Gelucire® 44/14 capsules or Melt-Extrusion tablets) and paclitaxel / carboplatin (TC) doublet which have an acceptable safety and tolerability profile, but are lower than the MTD, may be adopted for the dose expansion phase with the agreement between AstraZeneca and the investigators. These expansions will only be initiated upon agreement of the investigators or AstraZeneca dependant on the tolerability of the combination or other operational factors.

For patients with measurable disease, tumour evaluation (RECIST) will be conducted at the end of every 2 cycles up to 24 weeks then every 12 weeks and tumour markers (CA-153 for breast cancer patients and CA-125 for ovarian cancer patients) will be assessed at the end of each cycle. Patients who have at least stable disease and remain in the study after 6 cycles will be assessed in line with local clinical practice.

7.1.3 Randomised dose expansion phase

Up to two tolerable dose schedules selected from the dose escalation part IV of the study may be explored in a randomised expansion versus KU-0059436 (capsule formulation) at 200 mg bid days 1-10 of a 21 day cycle in combination with AUC 4 carboplatin and paclitaxel (175mg/m^2).

Approximately 45 patients will be recruited in this expansion (~15 patients per arm). The randomised dose expansion phase will only recruit female patients with metastatic breast cancer and patients with advanced ovarian cancer, where further treatment with platinum based chemotherapy is indicated.

The randomised dose expansion phase of the study will only be initiated after review of the safety, tolerability and operational feasibility of the regimen(s) by AstraZeneca and the Investigators.

Tumour evaluation (RECIST) will be conducted every 6 weeks, up to 24 weeks then every 12 weeks, and tumour markers (CA-153 for breast cancer patients and CA-125 for ovarian cancer patients) will be assessed at the end of each cycle.

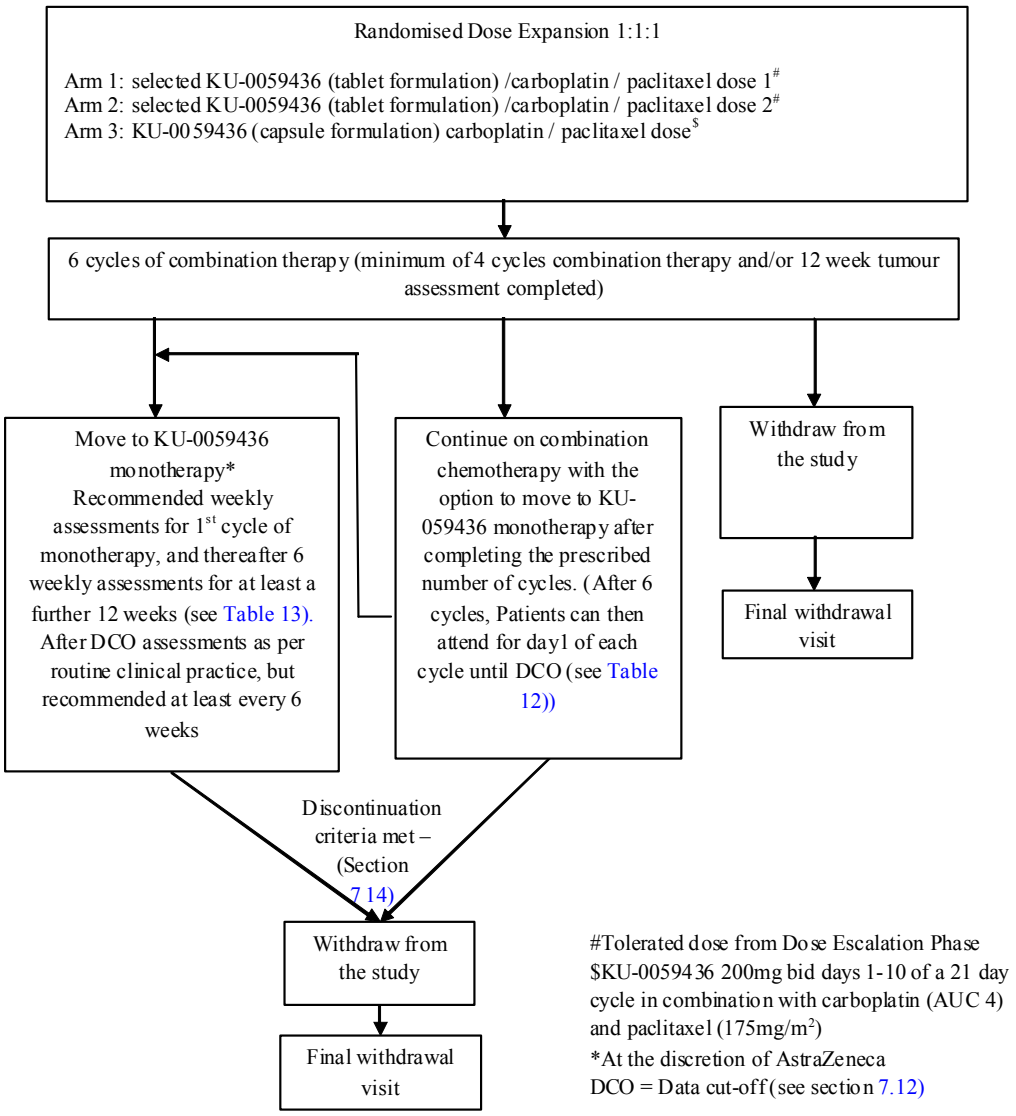
A patient may continue on monotherapy KU-0059436 (tablet or capsule) if in the investigator's opinion they are deriving clinical benefit from KU-0059436 treatment and have to stop carboplatin/paclitaxel treatment because they have completed the

prescribed course (minimum of 4 cycles) or due to toxicity.

Prior to receiving KU-0059436 monotherapy the tumour assessment at week 12 must be completed (unless otherwise agreed with AstraZeneca).

Patients in the randomised dose expansion phase who have been on treatment for over 6 cycles will continue to be seen by the investigator and have their safety assessments performed in accordance with Table 12. This data will be collected on the clinical database. When the last patient in the randomised dose expansion phase completes a minimum of 12 months of KU-0059436 monotherapy or there are no more patients remaining on treatment in the study, whichever is the earlier, the clinical study database will close to new data.

Figure 3: Flowchart to describe how to handle Patients in the Randomised Dose Expansion Phase



7.2 Number of Patients

It is expected that a maximum of approximately 250 patients will be enrolled in total.

In the dose escalation phase of the study, up to approximately 180 evaluable patients will be enrolled in the carboplatin and carboplatin / paclitaxel (TC) doublet arms.

Additionally, up to 12 evaluable patients will be enrolled in a comparator and parallel KU-0059436 + weekly paclitaxel dose escalation arm.

Additionally 15 female patients will be enrolled into a non-randomised dose expansion of a selected KU-0059436 / carboplatin / paclitaxel combination dose.

Other doses in the dose escalation phase deemed to be tolerated can be expanded in the non-randomised dose expansion to further assess tolerability. Up to 30 patients in

total can be included in these expansions.

A randomised expansion may be implemented to compare up to two selected KU-0059463 (tablet formulation)/ carboplatin / paclitaxel dose combination arms versus KU-0059436 (capsule formulation) at 200 mg bid days 1-10 of a 21 day cycle in combination with AUC 4 carboplatin and paclitaxel (175mg/m^2). Approximately 45 female patients may be enrolled in the randomised dose expansion phase of the study (~15 patients per arm). This sample size was based on obtaining a sufficient number of patients for comparisons of safety and, tolerability between the treatment arms.

7.3 Registration of Patients

7.3.1 Registration of patients to the study (in the non randomised phases)

Prior to registration, the patients must give written informed consent for the study and must complete all the pre-study evaluations described in section 9.2. Patients must meet all the eligibility requirements listed in section 6.0.

7.3.2 Randomisation of patients in the randomised expansion of the study

Prior to randomisation, the patients must give written informed consent for the study and must complete all the pre-study evaluations described in section 9.2. Patients must meet all the eligibility requirements listed in section 6.0. If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

7.4. Procedures for Randomisation

Randomisation codes will be assigned strictly sequentially, as patients become eligible for randomisation. Eligible patients will be randomised in a 1:1:1 ratio to either the up to 2 dosage arms of KU-0059436 (tablet formulation) in combination with paclitaxel/carboplatin or KU-0059436 (capsule formulation) at 200 mg bid days 1-10 of a 21 day cycle in combination with AUC 4 carboplatin and paclitaxel (175mg/m^2).

Randomisation will be stratified based on primary tumour type (breast cancer or ovarian cancer).

It is recommended that patients commence study treatment as soon as possible after randomisation, and ideally within 3 days.

A blocked randomisation will be generated and all centres will use the same list in order to minimise any imbalance in the number of patients assigned to each treatment group.

Patient eligibility will be established before treatment randomisation. Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should contact the IVR Centralised Randomisation Centre by telephone for allocation of randomised therapy.

Patients will be identified to the Centralised Randomisation Centre using patient initials, enrolment number and date of birth. If a patient discontinues participation in

the study, then their enrolment/randomisation code cannot be reused.

7.5 Procedures for handling patients incorrectly enrolled or randomised

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

Where patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post-initiation, the investigator should inform the AstraZeneca Global Study Delivery Team Physician immediately. The AstraZeneca Global Study Delivery Team Physician is to ensure all such contacts are appropriately documented.

7.6 Blinding and procedures for unblinding the study

Study treatment will not be blinded.

7.7 Treatment Dose and Schedule

Patients will receive prophylactic anti-emetic therapy before carboplatin administration according to local practice (i.e. 5HT3 antagonist plus dexamethasone). In addition all patients should be pre-medicated prior to paclitaxel dosing in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20mg PO administered approximately 12 and 6 hours before paclitaxel dosing, diphenhydramine (or its equivalent) 50mg iv 30-60 minutes before paclitaxel dosing, and cimetidine 300mg or ranitidine 50mg iv 30-60 minutes before paclitaxel.

7.7.1 Part I: KU-0059436 + 3- weekly carboplatin

KU-0059436 will be increased from 50mg twice-daily to at least 100mg twice daily over 2 cohorts of patients together with carboplatin AUC 4 unless dose limiting toxicity of the drug-combination occurs. If these combinations are tolerable then the dose of carboplatin will be increased to AUC 5 and KU-0059436 100mg twice daily, although if toxicity is noted, intermediate doses of carboplatin and KU-0059436 may be administered. If these combinations are tolerable then the dose of carboplatin will be increased to AUC 6 in combination with KU-0059436 which will be increased to a maximum 200mg twice daily over a further 2 cohorts. Although if significant toxicity is noted at any point in the escalation scheme, intermediate doses of carboplatin and KU-0059436 may be administered. A minimum of three patients must undergo repeated safety evaluations up to and including day 28 before enrolment can be commenced in to the next cohort. Decisions to escalate to the next level, or, when appropriate, to an intermediate dose level, will be made jointly by the investigators and sponsor's Responsible Medical Officer based on review of all the available data.

Table 1: Proposed dose escalation schedule for Part I: KU-0059436 + carboplatin

(other dose combinations may be tested)

1	4	50	3-6
2	4	100	3-6
3	5	100	3-6
4	6	100	3-6
5	6	200	3-6

The dose of carboplatin will be calculated based on the glomerular filtration rate (GFR) calculated using the following derived formulae dependent on the assay used to assess the serum creatinine (Wright JG, et al, 2001):

Using enzymatic serum creatinine:

$$GFR = \frac{(6230\text{-}32.8 \times Age) \times BSA \times (1\text{-}0.23 \times Gender)}{SCr}$$

Using Jaffe method serum creatinine:

$$GFR = \frac{(6580\text{-}38.8 \times Age) \times BSA \times (1\text{-}0.168 \times Gender)}{SCr}$$

Where: GFR = glomerular filtration rate ($ml min^{-1}$)
Age = Age in years
Gender = 1 for female, 0 for male
BSA = Dubois body surface area = $0.007184 \times weight^{0.425} \times height^{0.725}$
SCr = serum creatinine ($umol.l^{-1}$)

The GFR should then be used to calculate the dose of carboplatin using the Calvert formula (Calvert AH, *et al*,1989):

$$Dose\ (mg) = AUC\ (mg.ml^{-1}min^{-1}) \times (GFR\ (ml\ min^{-1}) + 25)$$

Based on FDA guidance (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm228974.htm), if a patient's GFR is estimated based on serum creatinine measurements by the IDMS method, FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Based on the Calvert formula described in the carboplatin label, the maximum doses can be calculated as:

For a target AUC = 6, the maximum dose is 6 x 150 = 900 mg
For a target AUC = 5, the maximum dose is 5 x 150 = 750 mg
For a target AUC = 4, the maximum dose is 4 x 150 = 600 mg

The maximum dose is based on a GFR estimate that is capped at 125 mL/min for

patients with normal renal function. No higher estimated GFR values should be used.

If one patient in a cohort of at least three patients experiences a DLT during the first cycle that is considered related to combination-therapy, excluding nausea, vomiting and alopecia, the cohort will be expanded to at least six patients.

Other dose combinations may be explored dependent upon emerging safety data. The KU-0059436 dose will not go below 50mg o.d. or above 400mg b.d. and the dose of carboplatin will not be reduced below AUC 4 or increased above AUC 6.

Pharmacokinetic (PK) evaluations will be performed on all patients and may be utilised to guide appropriate changes to the regimen, if indicated. KU-0059436 has the potential to generate haematological adverse events at high doses, and may exacerbate the toxicities observed with carboplatin.

Intra-patient dose escalations will not be permitted.

7.7.2 Part IIa: KU-0059436 + 3-weekly paclitaxel / carboplatin (TC) doublet

The starting doses for each drug will be;

- The maximum carboplatin dose that can be safely administered; established in Part I (AUC 4-6)
- KU-0059436, the maximum dose that can be safely administered; established in Part I (50-200mg b.d.)
- 90 mg/m^2 paclitaxel 3-weekly

If the initial dose combination with 90 mg/m^2 paclitaxel is well tolerated then the dose of paclitaxel will increase to 135mg/m^2 and finally to the standard 3 weekly dose of 175mg/m^2. If this dose combination is well tolerated then the carboplatin dose will be increased from the safe dose determined for carboplatin in Part I + AUC 1 with the paclitaxel / KU-0059436 dose remaining the same as the previous cohort. If these doses are well tolerated then the dose of carboplatin will increase up to AUC+2 of the initial Part IIa dose (up to a maximum of AUC 6). Subsequently, if the previous dose is well tolerated, the KU-0059436 dose will be doubled (up to a maximum dose of 400mg twice daily).

Intermediate doses of KU-0059436 or paclitaxel may be administered with carboplatin through dose escalations in order to obtain a safe combination with carboplatin AUC 5.

If one patient in a cohort of at least three patients experiences a DLT during the first cycle that is considered related to combination-therapy, excluding nausea, vomiting and alopecia, the cohort will be expanded to at least six patients.

Other dose combinations may be explored depending upon emerging safety data. The KU-0059436 dose will not go below 50mg o.d. or above 400mg b.d. and the dose of carboplatin will not be reduced below AUC 4 or increased above AUC 6. The dose of paclitaxel will not be lower than 90 mg/m^2 or higher than 175 mg/m^2.

Table 2 : Proposed dose escalation schedule for Part IIa: KU-0059436 + carboplatin + paclitaxel
(other dose combinations may be tested)

6	Carboplatin dose from part I	KU-0059436 dose from Part I	90 mg/m^2	3-6
7	Carboplatin dose from part I	KU-0059436 dose from Part I	135 mg/m^2	3-6
8	Carboplatin dose from part I	KU-0059436 dose from Part I	175 mg/m^2	3-6
9	Carboplatin dose from part I + AUC 1	KU-0059436 dose from Part I	175 mg/m^2	3-6
10	Carboplatin dose from part I +AUC 1	2 x KU-0059436 dose from Part I	175 mg/m^2	3-6
11	Carboplatin dose from part I +AUC 2	2 x KU-0059436 dose from Part I	175 mg/m^2	3-6
12	Carboplatin dose from part I +AUC 2	4 x KU-0059436 dose from Part I	175 mg/m^2	3-6

7.7.3 Part III: Discontinuous dose of KU-0059436 + paclitaxel / carboplatin (TC) doublet

The starting doses for each drug will be;

- The maximum carboplatin dose that can be safely administered; established in Part IIa (AUC 4-6)
- The maximum dose of KU-0059436 that can be safely administered in Part IIa (50-200mg b.d), given day 1 to day 10.

The maximum dose of paclitaxel that can be safely administered in Part IIa (90-175 mg/m^2) 3-weekly.

Table 3: Possible discontinuous dosing schedule for Part III: KU0059436 + paclitaxel + carboplatin ***(other dose combinations may be tested)***

1	AUC4	200mg b.d 10 days on 11 days off	175mg/m^2	3-6
2	AUC4	200mg b.d 2 days on 19 days off	175mg/m^2	3-6
3	AUC4	400mg b.d 2 days on 19 days off	175mg/m^2	3-6
3	AUC 5	400mg b.d 2 days on 19 days off	175mg/m^2	3-6

A discontinuous dose of KU-0059436 will be administered from day 1 to day 10 inclusive, but not from day 11 to day 21. The carboplatin dose will be AUC 4 and paclitaxel 175 mg/m^2.

Thereafter, other discontinuous KU-0059436 schedules consisting of KU-0059436 administered for pre-defined numbers of days, up to 20 days, may also be explored. A possible escalation scheme is presented in Table 3.

Further dose escalations of carboplatin, to an AUC of 6 and/or KU-0059436 (either in duration or in dose, to a maximum dose of 400mg b.d.) may also occur in conservative escalation steps based on review of the safety data of at least 3 patients of a cohort.

In addition dose de-escalations may be explored to determine a clinically feasible dose. These dose de-escalation cohorts may be conducted in parallel, providing the equivalent KU-0059436/carboplatin/paclitaxel dose was already explored and tolerated in earlier cohorts.

Additional cohorts of 3-6 patients will be recruited to Part III of the study to determine the tolerability of the 200mg bid Melt-Extrusion [tablet] formulation dose of KU-0059436 in conjunction with paclitaxel/carboplatin (TC). The KU-0059436 Melt-Extrusion [tablet] formulation and paclitaxel/carboplatin doses to be tested will be equivalent to a tolerable dose combination of the KU-0059436 Gelucire® 44/14 (capsule) and paclitaxel / carboplatin determined previously in this study.

Lower doses of the Melt-Extrusion tablet or different (previously tolerated) doses of carboplatin/paclitaxel may be tested dependant on emerging safety data, with the possibility of additional cohorts testing these doses if required.

The KU-0059436 dose will not go below 50mg o.d. or above 400mg b.d. and the dose of carboplatin will not be reduced below AUC 4 or increased above AUC 6. The dose of paclitaxel will not be lower than 90 mg/m^2 or higher than 175 mg/m^2.

At each new cohort, the duration and timing of the dosing will be decided upon review of the safety, tolerability and operational feasibility of the regimen adopted in previous cohorts, by the investigators and AstraZeneca. If one patient in a cohort of at least three patients experiences a DLT during the first cycle that is considered related

to combination-therapy, excluding nausea, vomiting and alopecia, the cohort will be expanded to at least six patients.

7.7.4 Part IV: Assessment of other discontinuous dose/schedules of KU-0059436 + paclitaxel / carboplatin (TC) doublet

If upon assessment of the first expansion cohort, it is determined by the investigator and AstraZeneca that from a tolerability point of view this dose/schedule is not appropriate for phase II/III studies, then part IV of the study will be opened to enable selection of an alternate dose/schedule.

In Part IV other discontinuous KU-0059436 schedules consisting of KU-0059436 (capsule or tablet) administered for any pre-defined numbers of days, up to 20 days, within each or specified treatment cycle maybe explored with carboplatin and paclitaxel. These cohorts (3-6 patients) may be recruited in parallel upon agreement of AstraZeneca and the investigators. The alternate schedules to be tested may include offsetting the start dose of KU-0059436 to day 2 or later, to avoid dosing KU-0059436 at the C_{max} of carboplatin, which may reduce toxicity. Other schedules that may be tested are alternating cycles of chemotherapy alone dosing and chemotherapy + KU-0059436, which may enable recovery from the toxicity due to the possible potentiating effect of KU-0059436 on carboplatin.

In addition within Part IV escalations or de-escalations of carboplatin or KU-0059436 may occur to determine the most effective dose. However, the dose of KU-0059436 will not go below 50mg o.d. or above 400mg b.d., the dose of carboplatin will not be increased above AUC 6 and the dose of paclitaxel will not be higher than 175 mg/m^2. Carboplatin and paclitaxel will be administered either on a 21 day or weekly schedule.

At each new cohort, the duration and timing of the dosing will be decided upon review of the safety, tolerability and operational feasibility of the regimen adopted in previous cohorts, by the investigators and AstraZeneca. Once suitable dose(s) are selected, randomised expansion will occur. This expansion may occur in parallel to ongoing escalation phase cohorts.

7.7.5 Randomised Dose Expansion Phase

After careful review of the Part IV cohort data, up to two KU-0059436 dose combinations consisting of KU-0059436 (tablet formulation) with carboplatin and paclitaxel may be selected by AstraZeneca and the investigators. Patients (approximately 15 per arm) will then be randomised to one of the following arms in a non blinded fashion:

Arm 1: selected KU-0059436 /carboplatin / paclitaxel dose 1

Arm 2: selected KU-0059436 /carboplatin / paclitaxel dose 2

Arm 3: KU-0059436 (capsule formulation) at 200mg bid days 1-10 of a 21 day cycle in combination with carboplatin (AUC 4) and paclitaxel (175mg/m^2)

7.7.6 Part IIb: KU-0059436 + Paclitaxel

KU-0059436 will be increased from 100mg twice-daily to at least 200mg twice-daily over 2 cohorts of patients together with 80mg/m^2 paclitaxel unless dose limiting

toxicity of the drug-combination occurs.

A minimum of three patients must complete cycle 1 in cohort 1 and undergo repeated safety evaluations up to and including day 35 before enrolment can be commenced in to the next cohort. Decisions to escalate to the next level, or, when appropriate, to an intermediate dose level, will be made jointly by the investigators and sponsor's Responsible Medical Officer based on review of all the available data.

If one patient in a cohort of at least three patients experiences a DLT during the first cycle that is considered related to combination-therapy, excluding nausea, vomiting and alopecia, the cohort will be expanded to at least six patients.

Table 4: Proposed dose escalation schedule for Part IIb: KU-0059436 + paclitaxel

1	100	80	3-6
2	200	80	3-6

7.8 Dose Limiting Toxicity

Toxicity will be graded using the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0. Dose-limiting toxicity (DLT) is defined as the following study drug-related events experienced during Cycle 1:

- Thrombocytopenia with platelets $<25{,}000 \times 10^6/l \geq 7$ days.
- Grade 4 neutropenia lasting ≥7 days.
- Grade 3 or 4 febrile neutropenia.
- Grade 3 or greater non-haematological toxicities; excluding grade 3 diarrhoea, nausea or vomiting despite adequate treatment and grade 3 fatigue, lethargy and GGT elevation.
- Delay of >2 weeks for next scheduled carboplatin or paclitaxel for reasons of toxicity.

Patients with dose-limiting toxicity after cycle 1 who have documented clinical benefit (stable disease or an objective response) may continue to be treated at a reduced dose level of carboplatin and paclitaxel and/or KU-0059436 if considered clinically appropriate by the investigator/AstraZeneca

Any patient in whom a DLT occurs during any cycle will have his or her KU-0059436, and/or carboplatin and/or paclitaxel treatment delayed until toxicity resolves to baseline or grade 1 or better. Scheduled treatment may be delayed up to 2 weeks to allow sufficient time for recovery from toxicities. Patients requiring a dose reduction will be dosed according to the guidance (Section 7.7).

7.9 Maximum Tolerated Dose

The Maximum Tolerated Dose (MTD) is defined as the prior or intermediate dose

level below the drug-combination that causes DLT, in at least 2 patients in a cohort of at least 3 patients who have completed one cycle of treatment.

If, at any dose level, a patient fails to complete cycle 1 for reasons other than DLT, that patient is deemed unevaluable for determining the MTD and may be replaced. Such a patient will be included in the evaluation of toxicity and efficacy.

It is also possible that a maximum dose that can be safely administered to patients will be determined (by AstraZeneca and investigators) prior to reaching the formal MTD.

7.10 Dose modifications in the KU-0059436 cohorts

Dose modification guidelines are set out below for the KU-0059436 cohorts and expansions.

7.10.1 Intra-patient Dose Modification in the KU-0059436 cohorts

In both the dose escalation and dose expansion phases of the study, after the safety evaluation at the end of cycle 1 (day 21), consideration may be given to dose reduction of KU-0059436, paclitaxel and carboplatin, based on the following guidelines.

Disease associated adverse events
For disease associated adverse events, treatments may be withheld for four weeks without the patient coming off study.

Drug toxicity
For drug associated toxicities the following will apply:

Initially delay all treatment until the toxicity has recovered based on guidance in Sections 7.10.2 – 7.10.6, followed by a single dose reduction to 50% of the KU-0059436 original dose, providing the dose does not fall below 50mg o.d (Gelucire® 44/14 capsule) or 50mg o.d (Melt-Extrusion tablet), based on guidance in Section 7.10.2. If after this 50% reduction, toxicity is still noted, then the KU-0059436 treatment duration may be halved eg. if KU-0059436 is being dosed between D1-10 the patient will reduce to KU-0059436 dosing between D1-5, if dosing between D1-5 they will reduce to D1-2 (7.7.1). However, if the patient is treated with KU-0059436 for 2 days or less (e.g. D1-2) the patient can then receive a reduction of carboplatin from AUC5 and AUC 6 to AUC 4 or AUC 5 carboplatin. If considered medically indicated, other types of dose reductions of KU-0059436, carboplatin or paclitaxel must be discussed with the AstraZeneca study physician first.

If administered, a single dose reduction of paclitaxel is allowed for subsequent cycles based on protocol guidance (Sections 7.10.5 and 7.10.6).

If administered, dose adjustments of carboplatin may be considered after a dose reduction of KU-0059436 after consultation with AstraZeneca.

Doses which have been reduced for toxicity must not be re-escalated.

The start date of cycles 2-6 may be delayed if the patient has not recovered from

treatment-emergent toxicities. A delay of >2 weeks will constitute a dose limiting toxicity.

7.10.2 Dose Modifications for Haematological Toxicity in the KU-0059436 cohorts

In the event of haematological toxicity (described below) all three drugs should be withheld until recovery from toxicity. The absolute neutrophil count (ANC) must be ≥1,500 x 10^6/l and the platelet count must be ≥100,000x 10^6/l in order to administer paclitaxel, carboplatin and KU-0059436 and administration is to be delayed until counts recover to those values. Table 5 summarises the required initial dose modifications or delays for patients who experience haematological toxicity that may be treatment-related.

Table 5: Dose Modifications for Haematological Toxicity

Dose Modifications for Thrombocytopenia	
Event	Action
Platelet Count <100,000 x 10^6/l on the day of scheduled treatment.	Delay the combination of paclitaxel (if dosed), carboplatin (if dosed) and KU-0059436 until platelet count ≥100,000 x 10^6/l.
If treatment delay of ≥7 days [#]	At the start of the next cycle reduce KU-0059436 by 50% to a minimum of 50mg o.d. (Gelucire® 44/14 capsule) or 50mg o.d (Melt-Extrusion tablet).
At any time following a dose of carboplatin:	
platelet count <50,000 x 10^6/l	No dose reduction. Delay the combination of paclitaxel (if dosed), carboplatin (if dosed) and KU-0059436 until platelet count ≥100,000 x 10^6/l.
platelet count <25,000 x 10^6/l [#]	Delay all treatment until platelet count ≥100,000 x 10^6/l and at the start of the next cycle reduce KU-0059436 by 50% to a minimum of 50mg o.d. (Gelucire® 44/14 capsule) or 50mg o.d (Melt-Extrusion tablet).

Dose Modifications for Neutropenia	
ANC of <1,500 x 10^6/l on any day of scheduled treatment.	Delay the combination of paclitaxel (if dosed), carboplatin (if dosed) and KU-0059436 until ANC ≥1,500 x 10^6/l.
If treatment delay of ≥7 days.[#]	At the start of the next cycle reduce KU-0059436 by 50% to a minimum of 50mg o.d. (Gelucire® 44/14 capsule) or 50mg o.d (Melt-Extrusion tablet).
At any time following a dose of carboplatin:	
• ANC of <1,000 x 10^6/l associated with hospitalisation or an emergency room visit for neutropenic fever or documented infection.[#]	Delay all treatment until ANC ≥1,500 x 10^6/l and at the start of the next cycle reduce KU-0059436 by 50% to a minimum of 50mg o.d. (Gelucire® 44/14 capsule) or 50mg o.d (Melt-Extrusion tablet).
• ANC of <500 x 10^6/l which lasts at least 5 days.[#]	Delay all treatment until ANC ≥1,500 x 10^6/l and at the start of the next cycle reduce KU-0059436 by 50% to a minimum of 50mg o.d. (Gelucire® 44/14 capsule) or 50mg o.d (Melt-Extrusion tablet).

[#]If there is a second toxicity or second ≥7 day delay in treatment after a reduction of the KU-0059436 dose by 50%, the following steps need to be taken:

1. If the patient is treated at AUC 4, 5, 6 carboplatin, the patient will halve the duration of the KU-0059436 dosing each cycle; if D1-10 they will reduce to D1-5, if D1-5 they will reduce to D1-2.

2. If the patient is treated with KU-0059436 for 2 days or less (e.g. D1-2) the patient will then receive a reduction of carboplatin from AUC 5 or AUC 6 to AUC 4 or AUC 5 carboplatin.

If considered medically indicated, other types of dose reductions of KU-0059436, carboplatin or paclitaxel must be discussed with the AstraZeneca study physician first.

Note: in the event of neutropenia (<500 x 10^6/l) and thrombocytopenia (<50,000 x 10^6/l) bloods **must** be taken more often than listed in the schedule of study evaluations, Table 9**,** Table 10, Table 11, Table 12 and Table 13, to establish the duration and nadir of neutropenia and thrombocytopenia.

7.10.3 Dose Modifications for Non-Haematological Toxicities in the KU-0059436 cohorts

Table 6: Dose Modifications for Non-Haematological Toxicities

Event	Action
Grade 2, 3 or 4 toxicity (excluding nausea, vomiting, alopecia and grade 2 diarrhoea, if not judged as clinically significant by the investigator) present on the day of scheduled treatment.	For grade 2 toxicity, delay all treatments until resolution to grade 1 or baseline. For grade ≥3 toxicity delay all treatments until resolution to grade 1 or baseline, then reduce KU-0059436 by 50% to a minimum of 50mg o.d. (Gelucire® 44/14 capsule) or 50mg o.d (Melt-Extrusion tablet)**.** Dependent on toxicity alterations in carboplatin (if dosed) and paclitaxel (if dosed) may be considered after consultation with AstraZeneca.

7.10.4 Dose reductions for patients continuing on monotherapy KU-0059436

Any toxicity observed during the course of monotherapy treatment on the study will be managed by interruption of the dose if deemed appropriate by the Investigator.

Repeat dose interruptions are to be allowed as required, for a maximum of 4 weeks (28 days) on each occasion. KU-0059436 must be interrupted until the patient recovers completely or the toxicity reverts to NCI-CTCAE grade 1 or less.

Where toxicity recurs following re-challenge with KU-0059436, and where further dose interruptions are considered inadequate for management of toxicity, then the patient is to be considered for dose reduction or must permanently discontinue treatment with KU-0059436.

Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 AE occurs which the Investigator considers to be related to administration of KU-0059436. If this has not resolved to at least NCI-CTCAE grade 1 during the maximum 4 weeks (28 days) dose interruption period, and/or the patient has already undergone the maximum number of dose reductions allowed (Table 7), the patient must permanently discontinue treatment with KU-0059436.

If toxicity is appropriately resolved, then the patient should restart treatment with KU-0059436, but with a dose reduction according to (Table 7). If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further dose reduction made (Table 7). If, on re-starting treatment, the event continues to occur, the patient must permanently discontinue KU-0059436.

Table 7 Dose reductions for KU-0059436 monotherapy

Reduction	Dose Level	Tablet
Initial Dose Level[a]	400 mg bid	200mg bid
1st dose reduction due to NCI-CTCAE grade 3 or 4 treatment related SAE/AEs	200mg bid	100mg bid
2nd dose reduction due to NCI-CTCAE grade 3 or 4 treatment related SAE/AEs	100mg bid	100mg od[b]
3rd Dose Reduction due to NCI-CTCAE grade 3 or 4 treatment-related SAEs/AEs.	No reduction allowed – withdraw patient	No reduction allowed – withdraw patient

[a] The starting dose is an example and may be different for individual patients
[b] KU-0059436 is not to be decreased below 100 mg b.d. for the capsule and 100 mg od for the tablet.

7.10.5 Carboplatin Dosing Modifications for Hypersensitivity Reactions

All patients will be carefully monitored for clinical features of hypersensitivity reactions. Should a hypersensitivity reaction of carboplatin occur during infusion, this must be discontinued and an attempt at desensitisation may be made subsequently if deemed appropriate by the investigator in discussion with the patient. The timing of this will be at the discretion of the investigator depending on the initial dose of carboplatin received.

Dexamethasone 8mg b.d. (total of 3 oral doses) should be given starting on the morning prior to administration, (i.e. morning, evening, morning). In addition, dexamethasone 8mg i.v. should be given 2 hours prior to carboplatin administration. Antiemetics should be given as usual (including dexamethasone 8mg i.v. and granisetron 1mg i.v.), together with chlorphenhydramine 10mg i.v. or clemastine 2mg immediately prior to administration.

Table 8: Dose Modifications for Hypersensitivity Reactions

Time (mins)	Dilution of full dosage	Diluted in	Example of amount of carboplatin administered at each level (based upon planned dose of 500mg)
0	1/500	100 ml 5% dextrose	1mg
+30	1/100	100 ml 5% dextrose	5mg
+60	1/10	100 ml 5% dextrose	50mg
+90	Remainder of planned dosage	500 ml 5% dextrose	444mg

The desensitisation procedure should take place with resuscitation facilities within easy access with regular observations and a trained nurse present throughout. If at any point during the dose escalation allergic signs or symptoms are documented, the carboplatin infusion must be discontinued.

All subsequent cycles should then be given using this procedure.

7.10.6 Paclitaxel Dose Modifications for Symptomatology of Severe Peripheral Neuropathy

In the event of the development of severe symptomatology of peripheral neuropathy, paclitaxel dosing alone should be delayed until recovery of severe symptomatology of peripheral neuropathy to grade 1, and subsequently a dose reduction to the next lowest paclitaxel dose will be required for all subsequent cycles. If the severe symptomatology of peripheral neuropathy continues after this reduction in paclitaxel, treatment must be withdrawn: carboplatin (if administered) and KU-0059436 can continue.

7.10.7 Paclitaxel Dosing Modifications for Hypersensitivity Reactions

Severe hypersensitivity reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angioedema, or generalised urticaria require the immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged. If patients are showing clinical benefit, dosing of carboplatin (if administered) and KU-0059436 can continue.

7.11 Duration of Study

Combination treatment with KU-0059436 and/or carboplatin/paclitaxel may continue for as long as the Investigator feels that the patient is receiving benefit and is free from intolerable toxicity. A patient may continue on monotherapy KU-0059436 (tablet or capsule) if in the investigator's opinion they are deriving clinical benefit from KU-0059436 treatment and have to stop carboplatin/paclitaxel treatment due to toxicity or because they have completed the prescribed course. If the patient is enrolled in the randomised dose expansion phase the tumour assessment at week 12 must be completed prior to receiving KU-0059436 monotherapy (unless otherwise agreed with AstraZeneca).

At the discretion of the PI and in consultation with AstraZeneca, the patient may receive up to the optimal recommended monotherapy dose, however once a dose is selected patients may not escalate the KU-0059436 again.

Patients in the dose escalation phase and patients in the non-randomised dose expansion phase of the study who have been on study treatment (either KU-0059436 alone or in combination with paclitaxel and/or carboplatin for over 6 cycles by the time of approval of protocol amendment 6, will have a final study assessment as per the Final Visit schedule (section 9.4). This will be the last data point recorded for each patient for the purpose of the clinical study. Patients who remain on KU-0059436 or carboplatin/paclitaxel after this time point will have assessments in line with the clinical protocol or as defined by local clinical practice.

Patients in the randomised dose expansion phase who have been on treatment for over 6 cycles will continue to be seen by the investigator and have their safety assessments performed in accordance with Table 12. This data will be collected on the clinical database. When the last patient in the randomised dose expansion phase completes a minimum of 12 months of KU-0059436 monotherapy or there are no more patients

remaining on treatment in the study, whichever is the earlier, the clinical study database will close to new data.

The investigator will continue to report SAEs for any patients still receiving treatment in the study to Theradex within 24hrs of becoming aware of the event up to and including 30 days after the patient stops receiving KU-0059436.

The overall duration of the study (defined as FSI to last patient stopping treatment) is anticipated to be approximately 8 years.

7.12 Data cut-off

For patients in the randomised dose expansion phase, CRF data will be collected until the last patient in the randomised dose expansion phase has completed a minimum of 12 months of KU-0059436 monotherapy, or there are no more patients remaining on treatment in the study, whichever is the earlier. The clinical database will then close to new data and the study data will be analysed and reported

Patients are permitted to continue to receive KU-0059436 or KU-0059436 in combination with carboplatin/paclitaxel beyond the closure of the clinical study database if, in the opinion of the investigator, they are continuing to receive benefit from treatment.

After the data cut-off, patients will continue to be monitored in line with the protocol defined visit schedule up to the last patient, or according to local clinical practice (but at least every 6 weeks until they meet any discontinuation criteria as per Section 7.14. Assessment information should still be collected in the patient's notes.

During these visits patients will be reviewed for SAEs. During the period of treatment with KU-0059436 or KU-0059436 + chemotherapy and up to 30 days after the last dose, all SAEs will continue to be reported to the sponsor's representative within 24 hours of the investigator becoming aware of the event.

Additionally any SAEs that are ongoing at the time of the closure of the clinical study database or any subsequent new SAEs must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve due to the underlying condition or the patient is lost to follow up..

At these routine clinic visits, patients will return used and unused medication, and a thorough drug accountability assessment will be performed.

7.13 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 stopped receiving KU-0059436 or KU-0059436 + carboplatin / paclitaxel

The overall duration of the study (defined as FSI to last patient stopping treatment) is anticipated to be approximately 8 years.

7.14 Removal of Patients from Therapy or Assessment

Patients will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and are not obliged to state their reasons. Additionally, the investigator may withdraw a patient at any time if he/she considers this to be in the patient's best interest.

Combination treatment with KU-0059436 and carboplatin / paclitaxel will continue for as long as the investigator feels that the patient is receiving benefit and is free from intolerable toxicity.

A patient may continue on monotherapy KU-0059436 (tablet or capsule) if in the investigator's opinion they are deriving clinical benefit from KU-0059436 treatment and have to stop carboplatin/paclitaxel treatment due to toxicity or because they have completed the prescribed course.

If the patient is enrolled in the randomised dose expansion phase the tumour assessment at week 12 must be completed prior to receiving KU-0059436 monotherapy (unless otherwise agreed with AstraZeneca).

At the discretion of the PI and in consultation with AstraZeneca, the patient may receive up to the optimal recommended monotherapy dose. If carboplatin/paclitaxel is permanently discontinued, patients will continue with study assessments as defined in section 9.7.

The patient **must** be discontinued from the study for the following reasons:

- Disease progression
- Intolerable or unresolved toxicity
- Withdrawal of patient consent.
- Non-compliance with protocol.
- Life-threatening toxicity.
- Investigator discretion.

If a patient fails to return for a scheduled visit/follow up, attempts should be made to contact the patient to ensure that the reason for not returning is not an adverse event (AE). Likewise if a patient declares his/her wish to discontinue from the study, e.g. for personal reasons, an attempt should be made to establish that the true reason is not an AE (bearing in mind the patient is not obliged to state his/her reasons). If the study drug therapy is prematurely discontinued the primary reason for discontinuation must be recorded in the appropriate section of the case report form (CRF) and all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation following the patient's withdrawal should be made, and any AEs followed up until resolution unless in the opinion of the investigator the condition is unlikely to resolve due to the patients underlying disease (see sections 11.4.6 and 11.4.8).

Except for patients in the randomised dose expansion phase, non-serious adverse events will be collected from the time consent is given, up to completion of the Final Visit after 6 cycles of treatment or the approval of amendment 6 (whichever is last). SAEs will be collected from the time consent is given, throughout the treatment period and up to and including the 30 day follow-up period after the last dose of investigational product. For patients remaining on study following 6 cycles of treatment or after approval of protocol amendment 6, or if they have withdrawn prior to cycle 6 at 30 days after the last dose of study drug, patients will be assessed for any SAEs or ongoing SAEs. Follow-up of SAEs should be pursued until either the event has returned to the baseline grade (for pre-existing conditions); or until: the SAE is determined to be chronic in the opinion of the investigator and the condition is unlikely to resolve due to the patient's underlying disease or the patient is lost to follow-up. Additionally, any SAE that the Investigator considers related to the study treatment occurring later than 30 days after the last study drug administration will also be reported to Theradex.

For patients in the randomised dose expansion phase, non-serious adverse events will be collected from the time consent is given, up to the data cut-off (see section 7.12). SAEs will be collected from the time consent is given, throughout the treatment period and up to and including the 30 day follow-up period after the last dose of investigational product.
Follow-up of SAEs should be pursued until either the event has returned to the baseline grade (for pre-existing conditions); or until: the SAE is determined to be chronic in the opinion of the investigator and the condition is unlikely to resolve due to the patient's underlying disease or the patient is lost to follow-up. Additionally, any SAE that the Investigator considers related to the study treatment occurring later than 30 days after the last study drug administration will also be reported to Theradex.

7.15 Concomitant Therapy

Patients are allowed to receive supportive care therapies (excluding cytokine growth factors) concomitantly during the study. No other chemotherapy, immunotherapy, hormonal cancer therapy (with the exception of bisphosphonates for bone disease and corticosteroids provided the dose is stable before and during the study), radiation therapy (except small field radiotherapy with palliative intent) or experimental medications are permitted during the study, or if possible for up to four weeks after the last KU-0059436 dose (unless otherwise agreed with AstraZeneca).

Any disease progression that requires other specific anti-tumour therapy will be cause for discontinuation from the study.

The following concomitant therapies warrant special attention:

KU-0059436 is an investigational drug, for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data KU-0059436 is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of KU-0059436 is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety the following potent inhibitors of CYP3A4 must not be used during this

study for any patient receiving KU-0059436.

Whilst this is not an exhaustive list, it covers the known potent inhibitors which have most often previously been reported to be associated with clinically significant drug interactions:

Ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin (wash-out period 1 week).

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4 inducers are excluded:

Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone and St John's Wort (wash-out period for phenobarbitone 5 weeks and for any of the others 3 weeks).

Caution should be exercised in the concomitant use of amino-glycosides with carboplatin, as this may result in increased renal and/or audiologic toxicity.

Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either cytochrome P450 isoenzymes CYP2C8 or CYP3A4 (e.g. erythromycin, fluoxetine, gemfibrozil).

If use of any potent inducers or inhibitors of P450, CYP2C8 or CYP3A4 are considered necessary for the patient's safety and welfare, the Investigator must contact the Theradex Medical Advisor, and a decision to allow the patient to remain on study will be made on a case-by-case basis.

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

Anticoagulant Therapy: Patients who are taking low dose warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

Anti-emetics: Prophylactic anti-emetic therapy where indicated.

Colony Stimulating Factors: The routine use of granulocyte colony stimulating factors (G-CSF) is not permitted during this study. In particular G-CSF should not be administered in cycle 1 either prophylactically or for uncomplicated neutropenia while assessing DLT potential. G-CSF may however be used therapeutically if clinically indicated, e.g. complicated neutropenia. Patients who are on recombinant human erythropoietin prior to study entry may continue on this therapy. The use of recombinant erythropoietin for patients not currently receiving erythropoietin and who have symptomatic anaemia during treatment may be considered upon discussion with the principal investigators.

All medications (prescriptions or over-the-counter medications) continued at the start of the study or started during the study or until 30 days from the end of the last

protocol treatment and different from the study medication must be documented.

8.0 PHARMACEUTICAL INFORMATION

8.1 KU-0059436 Delivery, Stability and Storage

Gelucire® 44/14 (capsule)

The study drug KU-0059436 is available in 10mg and 50mg size 0 capsules.

Melt-Extrusion [tablet] formulation

The study drug is also available in green, film-coated tablets containing either 25 mg or 100 mg KU-0059436.

The capsules and tablets will be supplied in white high density polyethylene (HDPE) containers with child-resistant closures.

The assembly of long term stability data continues. KU-0059436 tablets and capsules should not be refrigerated. For shelf life and storage conditions, see drug label.

8.2 KU-0059436 Accountability/Disposal

Patients will self-administer KU-0059436 capsules or tablets. A member of the Investigative site's study team will query the patient for treatment compliance at each visit. All patients must return their bottle(s) of KU-0059436 at the end of each scheduled treatment cycle, when (a) new bottle(s) will be dispensed. An assessment of compliance (capsule/tablet count) of any remaining capsules/tablets in the bottle will be performed in order to determine if the patient is following their treatment dose schedule. Compliance will be assessed by the capsule/tablet count and the information will be recorded in the appropriate section of the Case Report Form (CRF). After the capsule/tablet count has been performed, the remaining capsules/tablets will not be returned to the patient but will be retained by the Investigative site until the study monitor completes reconciliation.

Any unused supply of KU-0059436 capsules/tablets will be returned to AstraZeneca or its representative upon completion of the study or destroyed at site following written approval from AstraZeneca.

8.3 Carboplatin Delivery, Stability and Storage

It is expected that centres will use their commercial supply of carboplatin for this study. In situations where the cost of the drug is not covered by third party payment, (i.e. insurance) then centres will be reimbursed for the cost of the drug. Carboplatin should be stored, reconstituted and administered according to the manufacturer's recommendation. Details of each dose administered and the duration of infusion must be recorded in the CRFs.

8.4 Carboplatin Accountability

The responsible pharmacist will track all carboplatin allotted to the study and administered to the study patients.

8.5 Paclitaxel Delivery, Stability and Storage

It is expected that centres will use their commercial supply of paclitaxel for this study. In situations where the cost of the drug is not covered by third party payment, (i.e. insurance) then centres will be reimbursed for the cost of the drug. Paclitaxel should be stored, reconstituted and administered according to the manufacturer's recommendation. Details of each dose administered and the duration of infusion must be recorded in the CRFs.

8.6 Paclitaxel Accountability

The responsible pharmacist will track all paclitaxel allotted to the study and administered to the study patients.

8.7 KU-0059436 / Carboplatin / Paclitaxel Preparation and Administration

KU-0059436 is supplied as Hydoxypropyl Methylcellulose (HPMC) white (50mg) capsules and red (10mg) capsules to be taken orally or the KU-0059436 Melt-Extrusion [tablet] formulation is green, film-coated tablets containing either 25 mg or 100 mg. Patients should swallow the medication whole with a glass of water during the morning and evening (or in the morning for once daily dosing) at the same times every day. This is to ensure a dose interval of approximately 12 hours. For days in which patients will be providing PK samples they should have a light meal 3 hours before dosing and refrain from eating for at least 2 hours post dose. (For patients in the randomised dose expansion phase who have moved to monotherapy KU-0059436, see section 10.1.1 for details).

Carboplatin and paclitaxel infusion will be prepared in line with normal clinical procedures and the prescribing information.

Part I
Carboplatin will be administered on day 8 of cycle 1 (28 day cycle) and on day 1 of all other cycles. It should be administered at least 1 hour after the patient has taken their KU-0059436.

Part IIa
Carboplatin and paclitaxel will be administered on day 8 of cycle 1 (28 day cycle). Paclitaxel will be administered in a 3-hour infusion at least 1 hour after KU-0059436 administration. This will be followed by a carboplatin infusion.

For all other cycles, paclitaxel followed by carboplatin will be administered on day 1 of a 21-day cycle.

Part IIb
Paclitaxel will be administered on days 8, 15 and 22 of cycle 1 (35 day cycle) and on days 1, 8 and 15 of all other cycles (28 days). Paclitaxel will be administered in a 3-

hour infusion at least 1 hour after KU-0059436 administration.

Part III
Carboplatin and paclitaxel will be administered on day 1 of cycle 1 (21 day cycle). Paclitaxel will be administered in a 3-hour infusion at least 1 hour after KU-0059436 administration. This will be followed by a carboplatin infusion.

Part IV
Carboplatin and paclitaxel will be administered on day 1 of cycle 1 (21-day cycle) or weekly on a weekly cycle. Paclitaxel will be administered in a 3-hour infusion, which will be followed by a carboplatin infusion. KU-0059436 may be administered for pre-defined numbers of days, up to 20 days with defined rest periods within each or specified treatment cycles. The start date of dosing will be determined by AstraZeneca and the investigators.

Randomised dose expansion phase

In the KU-0059436 dose combination arms, carboplatin and paclitaxel will be administered on day 1 (21 day cycle) or weekly on a weekly cycle. Paclitaxel will be administered in a 3-hour infusion which will be followed by a carboplatin infusion. KU-0059436 may be administered for pre-defined numbers of days, up to 20 days with defined rest periods, within each or specified treatment cycles. The start date of dosing will be determined by AstraZeneca and the investigators.

In the comparator arm, KU-0059436 (capsule formulation) at dose 200mg bid days 1-10 (21 day cycle) in combination with carboplatin (AUC 4) and paclitaxel ($175mg/m^2$) will be administered on day 1 of cycle 1 (21 day cycle).

Paclitaxel will be administered in a 3-hour infusion at least 1 hour after KU-0059436 administration. This will be followed by a carboplatin infusion.

9.0 SCHEDULE OF ASSESSMENTS, INVESTIGATIONS AND SAMPLING

In Parts I and IIa, the first cycle of treatment is scheduled to last 4 weeks (28 days – cycle 1). All other cycles will be 21 days long. In Part III all cycles will be 21 days long. In Part IIb, cycle 1 will be 35 days duration and all other cycles will be 28 days duration. For details of the schedule and nature of the assessments, see below.

The patient's assessments will consist of:

9.1 Informed Consent

Each potentially eligible patient will be informed of the study's objectives and overall requirements. Prior to conducting any of the pre-entry tests not performed routinely in standard patient treatment, the investigator will explain the study fully, using the Patient Informed Consent Documents (PICD). If the patient is willing to participate in the study they will be requested to give written informed consent, after having been given sufficient time for consideration, and the opportunity to ask for any further details. The Informed Consent will be signed and personally dated by both the patient and the investigator. A copy of the signed form will be provided to the patient and the

original retained with the source documents. Although nursing staff may be involved in describing the study to a patient, the investigator must participate in discussions with the patient and sign and personally date the Informed Consent documentation.

A "pre-study screening" log will be completed for all patients who signed the Informed Consent but who did not subsequently enter the study. Patients will be identified by their initials and date of birth. In addition, their reasons for exclusion from the study will be recorded.

9.2 Baseline/pre-study (applies to escalation Parts I, IIa, IIb, III and IV, and dose expansion including randomised phase)

Baseline examinations should be performed as close to the first day of dosing with investigational product as possible and the interval should not exceed 7 days except for radiological studies, where a period of up to 4 weeks prior can be permissible.

Within 4 weeks prior to study dosing:

- Tumour evaluation (RECIST)

Within 7 days prior and as close to the first dose as possible:

- Review of inclusion/exclusion criteria.
- Medical history including the history of the neoplastic disease, previous therapy, pre-existing diseases and current medication.
- Physical examination including measurements of height, weight and body surface area.
- ECOG performance status.
- Concomitant medication and adverse events from time of consent.
- Vital signs (heart rate, blood pressure, respiratory rate and temperature).
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets. Patients on the randomised dose expansion phase will also require TSH, B12, homocysteine and folate.
- Coagulation: INR and APTT.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- Markers: CA-125 for ovarian patients and CA-153 for breast patients.
- Urinalysis: Dipstick for albumin, glucose, bilirubin and blood (microscopy if more than one positive test).
- Biomarkers: Blood and urine samples for potential retrospective analysis, if consent is obtained.
- Calculated creatinine clearance (Jaffe or enzymatic serum creatinine) (within 7 days prior to commencing carboplatin).

- Calculated Glomerular Filtration Rate (GFR) (within 7 days prior to commencing carboplatin).
- ECG.
- Urine **or** serum pregnancy test for females of reproductive potential.
- Chest X-ray
- Pharmacogenetic blood sample (optional): 9ml Blood sample to be collected. DNA will be extracted and stored for possible future analysis, subject to patient consent.

9.3 On Study Sampling and Assessment

Dose Escalation Phase Part I and Part IIa

The details of the required investigations are explained in the following sections and the study plan is shown in Table 9.

Examinations marked with (*) need not be repeated if already performed within 3 days:

Cycle 1

Day 1

- *Review of inclusion/exclusion criteria.
- * Review of medical history including baseline symptoms.
- Review of AEs and current medication.
- * Brief physical examination including weight and description of external signs of neoplastic disease.
- * ECOG performance status.
- Vital signs (including heart rate, blood pressure, respiratory rate and temperature).
- * Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- * Biomarkers.
- * CA-125 for ovarian patients and CA-153 for breast patients.
- * Coagulation: INR and APTT.
- * Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- * Urinalysis: Dipstick for albumin, glucose, bilirubin and blood (microscopy if any more than one positive test).
- * ECG.
- *Chest X-ray
- * Urine or serum pregnancy test for females of reproductive potential.
- Pharmacogenetic blood sample (optional): 9ml Blood sample to be collected (if not done at the baseline visit).
- Commence daily oral administration of KU-0059436.

- The Patient Medication Record must be completed on each day of KU-0059436 intake.

Day 4 (only for dose escalation phase)
- PK sampling KU-0059436 (pre-dose and up to 8 hours post-dose).

Day 8
- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate temperature and weight).
- * Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- * Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- PK sampling KU-0059436 (dose escalation phase only).
- Carboplatin and paclitaxel PK samples (dose escalation phase only)
- Administer carboplatin alone (Part I) or paclitaxel followed by carboplatin (Part II and expansion). In Part I carboplatin will be administered intravenously at least 1 hour after KU-0059436 capsules taken. In Part IIa and dose expansion phase paclitaxel will be administered intravenously at least 1 hour after KU-0059436 capsules taken, with carboplatin administered after the completion of the 3 hour paclitaxel infusion.
- KU-0059436 daily dosing continues.

Day 9
- Carboplatin and paclitaxel PK sample taken 24 hours after carboplatin and paclitaxel were first administered respectively (dose escalation phase only).

Day 10
- Carboplatin PK sample (dose escalation phase only)

Day 15
- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets (weekly).
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- KU-0059436 daily dosing continues.

Day 22
- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials,

absolute neutrophil count, lymphocytes and platelets (weekly).
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- KU-0059436 daily dosing continues.

Day 28
- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets (weekly).
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).

Cycle 2 and all subsequent cycles

Day 1 (prior to treatment)

- Review of AEs and current medication.
- Physical examination including weight.
- ECOG performance status.
- Vital signs (including heart rate, blood pressure, respiratory rate temperature and weight).
- * Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Coagulation: INR and APTT.
- * Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]). (Repeat within cycle when clinically indicated).
- CA-125 for ovarian patients and CA-153 for breast patients.
- Calculated creatinine clearance (Jaffe or enzymatic serum creatinine).
- Urinalysis.
- Commence daily oral administration of KU-0059436.
- Administer carboplatin alone (Part I) or paclitaxel followed by carboplatin (Part IIa and expansion). In Part I carboplatin will be administered intravenously at least 1 hour after KU-0059436 capsules taken. In Part IIa and dose expansion phase paclitaxel will be administered intravenously at least 1 hour after KU-0059436 capsules taken, with carboplatin administered after the completion of the 3 hour paclitaxel infusion.

Day 8
- Review of AEs and current medication.
- Vital signs.

- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- KU-0059436 daily dosing continues.

Day 15
- Review of AEs and current medication.
- Vital signs.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- KU-0059436 daily dosing continues.

Day 21
- Tumour evaluation. Every 2 cycles until week 24 then every 12 weeks until confirmed progressive disease.
- Biomarkers. Cycle 2 only.

If treatment is delayed or patient is to be withdrawn the following evaluations will be performed.
- Review of AEs and current medication.
- Vital signs.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.

Dose Escalation Phase Part III, Part IV, patients continuing on monotherapy KU-0059436 and Dose Expansion including Randomised Dose Expansion Phase

The details of the required investigations are explained in the following sections and the study plan is shown in Table 10.

Examinations marked with (*) need not be repeated if already performed within 3 days:

Cycle 1 and subsequent cycles

Day 1
- * Review of inclusion/exclusion criteria (only in cycle 1).
- * Review of medical history including baseline symptoms (only in cycle 1).
- Review of AEs and current medication.
- * Brief physical examination including weight and description of external signs of neoplastic disease.
- * ECOG performance status.
- Vital signs (including heart rate, blood pressure, respiratory rate and temperature).
- * Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets. In addition, for patients in the randomised dose expansion phase, TSH, B12. homocysteine and folate are required.
- * Biomarkers (only in cycle 1).
- * CA-125 for ovarian patients and CA-153 for breast patients.
- * Coagulation: INR and APTT.
- KU-0059436 PK sampling (pre-dose and up to 8 hours post-dose - only in dose

escalation phase cycle 1).

- * Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- * Urinalysis: Dipstick for albumin, glucose, bilirubin and blood (microscopy if any more than one positive test).
- * ECG.
- *Chest X-ray
- Pharmacogenetic blood sample (optional): 9ml Blood sample to be collected (if not done at the baseline visit).
- * Urine or serum pregnancy test for females of reproductive potential (cycle 1 only).
- Calculated creatinine clearance (Jaffe or enzymatic serum creatinine; cycle 2 onwards).
- PBMC pharmacodynamic sampling (cycle 1 and 2 only see Section 10.2.1 for details).
- In randomised expansion only – call the Centralised Randomisation Centre
- Commence twice daily oral administration of KU-0059436
- Paclitaxel and carboplatin administration. Paclitaxel will be administered intravenously at least 1 hour after intake of KU-0059436 capsules/tablets, with carboplatin administered after the completion of the 3 hour paclitaxel infusion.
- The Patient Medication Record must be completed on each day of KU-0059436 intake.

Day 2

- PBMC pharmacodynamic samples to be taken pre KU-0059436 dose (see Section 10.2.1 for details).
- KU-0059436 PK sample to be taken pre KU-0059346 dose (close to the time of the PBMC sample).

Day 8

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate temperature and weight).
- * Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- * Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- PBMC pharmacodynamic samples taken any time on day 8(see Section 10.2.1 for details). $
- KU-0059436 PK samples to be taken any time on day 8, close to the time of the PBMC samples.$
- KU-0059436 twice daily dosing continues (dependant on schedule).
- Paclitaxel and/or carboplatin administration if on a weekly cycle. Paclitaxel will be administered intravenously at least 1 hour after intake of KU-0059436

capsules/tablets, with carboplatin administered after the completion of the 3 hour paclitaxel infusion.

Day 10-Day 12

- PBMC pharmacodynamic samples to be taken any time between day 10 and day 12 (see Section 10.2.1 for details)$.

Day 15

- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets (weekly).
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- PBMC pharmacodynamic samples taken any time on day 15 (see Section 10.2.1 for details).
- Paclitaxel and/or carboplatin administration if on a weekly cycle. Paclitaxel will be administered intravenously at least 1 hour after intake of KU-0059436 capsules/tablets, with carboplatin administered after the completion of the 3 hour paclitaxel infusion.

Day 18

- $If KU-0059436 dosing is extended to 8 days or beyond, then a PD/PK sample will be collected on Day 18 of cycle 1. The day 2 and day 8 PD/PK samples will not be collected.

Day 21

- Tumour evaluation. Every 2 cycles until week 24 then every 12 weeks until confirmed progressive disease.
- Biomarkers (only in cycle 2).

If treatment is delayed or patient is to be withdrawn the following evaluations will be performed.

- Review of AEs and current medication.
- Vital signs.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.

Dose Escalation Phase Part IIb

The details of the required investigations are explained in the following sections and the study plan is shown in Table 11.

Examinations marked with (*) need not be repeated if already performed within 3 days:

Cycle 1

Day 1

- * Review of inclusion/exclusion criteria.
- * Review of medical history including baseline symptoms.
- Review of AEs and current medication.
- * Brief physical examination including weight and description of external signs of neoplastic disease.
- * ECOG performance status.
- Vital signs (including heart rate, blood pressure, respiratory rate and temperature).
- * Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- * Biomarkers.
- * CA-125 for ovarian patients and CA-153 for breast patients.
- * Coagulation: INR and APTT.
- * Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- * Urinalysis: Dipstick for albumin, glucose, bilirubin and blood (microscopy if any more than one positive test).
- * ECG.
- * Chest X-ray
- Pharmacogenetic blood sample (optional): 9ml Blood sample to be collected (if not done at the baseline visit).
- * Urine or serum pregnancy test for females of reproductive potential.
- Commence twice daily oral administration of KU-0059436.
- The Patient Medication Record must be completed on each day of KU-0059436 intake.

Day 4

- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- PK sampling KU-0059436 (pre-dose and up to 8 hours post-dose).

Day 8

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate temperature and weight).
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT],

urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- PK sampling KU-0059436.
- Paclitaxel PK samples.
- Administer paclitaxel intravenously at least 1 hour after KU-0059436 capsules taken.
- KU-0059436 twice daily dosing continues.

Day 9
- Paclitaxel PK sample taken 24 hours after paclitaxel was first administered.

Day 11
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).

Day 15
- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets (weekly).
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- Administer paclitaxel intravenously at least 1 hour after KU-0059436 capsules taken.
- KU-0059436 twice daily dosing continues.

Day 18
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).

Day 22
- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets (weekly).
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose,

creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- Administer paclitaxel intravenously at least 1 hour after KU-0059436 capsules taken.
- KU-0059436 twice daily dosing continues.

Day 25
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).

Day 28
- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets (weekly).
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).

Day 31
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).

Day 35
- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets (weekly).
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).

Cycle 2 and all subsequent cycles

[$] Cycle 2 only unless indicated thereafter.

Day 1 (prior to treatment)

- *Review of AEs and current medication.
- Physical examination including weight.
- ECOG performance status.
- Vital signs (including heart rate, blood pressure, respiratory rate temperature and weight).
- * Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Coagulation:INR and APTT.
- * Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- CA-125 for ovarian patients and CA-153 for breast patients.
- Urinalysis.
- Commence twice daily oral administration of KU-0059436.
- Administer paclitaxel intravenously at least 1 hour after KU-0059436 capsules taken.

Day 4[$]

- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).

Day 8

- Review of AEs and current medication.
- Vital signs.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- KU-0059436 twice daily dosing continues.
- Administer paclitaxel intravenously at least 1 hour after KU-0059436 capsules taken.

Day 11[$]

- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.

- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).

Day 15

- Review of AEs and current medication.
- Vital signs.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- KU-0059436 twice daily dosing continues.
- Administer paclitaxel intravenously at least 1 hour after KU-0059436 capsules taken.

Day 18[$]

- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).

Day 21

- Review of AEs and current medication.
- Vital signs.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).

Day 25[$]

- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).

Day 28

- Tumour evaluation. Every 2 cycles until week 24 then every 12 weeks until confirmed progressive disease.
- Biomarkers. Cycle 2 only.

If treatment is delayed or patient is to be withdrawn the following evaluations will be performed.

- Review of AEs and current medication.
- Vital signs.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.

Throughout study: If clinically indicated a bone marrow biopsy will be taken from the patient according to local procedures. This sample will be analysed locally to determine any potential effect of KU-0059436 on bone marrow progenitor cells to further understand the mechanism of any KU-0059436 toxicity.

9.4 Final visit/withdrawal visit (applies to dose escalation Parts I, IIa, IIb III, IV and non-randomised dose expansion phase)

The final visit is to occur after 6 cycles of treatment or approval of amendment 6 (whichever is last)

- Review of AEs and concurrent medication.
- Physical examination including description of external signs of the neoplastic disease.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature and weight).
- ECOG performance status.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- Urinalysis: Dipstick for albumin, glucose, bilirubin and blood (microscopy if more than one positive test).
- Tumour evaluation.
- ECG.
- Chest X-ray.

9.5 Final Visit/Withdrawal Visit – Randomised Dose Expansion only

Patients in the randomised dose expansion phase will continue to have their assessments conducted in accordance with Table 12, until the data cut-off (see section 7.12)

Prior to the data cut-off, if a patient withdraws from the study due to meeting the discontinuation criteria (section 7.14), a withdrawal visit should be performed and the

data collected in the CRFs.

If the patient withdraws from study after the data cut-off, the withdrawal visit should be performed, but the details should be recorded in the patient's notes and not captured in the CRFs.

The following assessments are expected to be performed at the withdrawal visit:

- Review of AEs and concurrent medication.
- Physical examination including description of external signs of the neoplastic disease.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature and weight).
- ECOG performance status.
- Haematology: haemoglobin, haematocrit, MCV, leukocyte count, differentials, absolute neutrophil count, lymphocytes, platelets, TSH, B12, homocysteine and folate
- Blood chemistry: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]).
- Urinalysis: Dipstick for albumin, glucose, bilirubin and blood (microscopy if more than one positive test).
- Tumour evaluation.
- ECG.
- Chest X-ray.

9.6 Follow-Up

A final Follow-up Visit should be conducted 30 days after the last dose of the study treatment(s). Physical examination, haematology and biomarker will be assessed. Any serious and/or non-serious AEs ongoing at the time of the Withdrawal Visit or which have occurred since the last dose of study treatment(s) must be followed-up (in accordance with Section 11.4.6) and appropriate safety evaluations repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator. If the patient is lost to follow up, then this should be noted in the CRF.

9.7 Patients Continuing on Therapy (applies to dose escalation Parts I, IIa, IIb, III, IV and Non-Randomised Dose Expansion Phase)

This section applies to patients continuing on KU-0059436 or combination KU-0059436 + chemotherapy after 6 cycles of treatment or approval of protocol amendment 6 (whichever is last):

Any patient, who in the opinion of the Investigator is obtaining a clinical benefit and is tolerating the treatment well after the Final Visit after 6 cycles of treatment, or approval of amendment 6 (whichever is last) may continue to receive KU-0059436 or the combination chemotherapy until such time that a clinical benefit is not apparent.

These patients will continue to be monitored in line with the protocol defined visit schedule or according to local clinical practice and during these visits patients will be reviewed for SAEs. During the period of treatment with KU-0059436 or KU-0059436 + chemotherapy and up to 30 days after the last dose, all SAEs will continue to be reported to the sponsor's representative within 24 hours of the investigator becoming aware of the event.

Additionally any SAEs that are ongoing at the time of the closure of the clinical study database or any subsequent new SAEs must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve due to the underlying condition or the patient is lost to follow up.

At these routine clinic visits, patients will return used and unused medication, and a thorough drug accountability assessment will be performed. If patients continue to derive clinical benefit while tolerating the treatment well, patients will continue on treatment at the investigator's discretion

9.8 Patients Continuing on Therapy –Randomised Dose Expansion Phase

Any patient, in the randomised dose expansion phase, who in the opinion of the Investigator is obtaining a clinical benefit and is tolerating the treatment well may continue to receive KU-0059436 or KU-0059436 + chemotherapy until such time that a clinical benefit is not apparent.

After the patients have received 6 cycles of treatment, the patients will continue to have their safety assessments monitored as defined with the protocol visit schedule, up to the data cut-off (see Section 7.12).

After the data cut-off, patients will continue to be monitored in line with the protocol defined visit schedule (see Table 12) up to the last patient, or according to local clinical practice and during these visits patients will be reviewed for SAEs. During the period of treatment with KU-0059436 and/or chemotherapy and up to 30 days after the last dose, all SAEs will continue to be reported to the sponsor's representative within 24 hours of the investigator becoming aware of the event.

Additionally any SAEs that are ongoing at the time of the closure of the clinical study database or any subsequent new SAEs must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve due to the underlying condition or the patient is lost to follow up..

At these routine clinic visits, patients will return used and unused medication, and a thorough drug accountability assessment will be performed.

9.9 Visit Schedule for Patients Continuing on Monotherapy KU-0059436 (Dose escalation and non-randomised dose expansion phases)

A patient may continue on monotherapy KU-0059436 (tablet or capsule) if in the investigator's opinion they are deriving clinical benefit from KU-0059436 treatment and have to stop carboplatin/paclitaxel treatment due to toxicity or because they have completed the prescribed course. If the patient continues on KU-0059436 alone, at the

discretion of the PI and in consultation with AstraZeneca, the patient may receive up to the optimal recommended monotherapy dose. Once a dose is agreed for the patient no further dose escalations will be allowed.

When carboplatin/paclitaxel is permanently discontinued and patients initiate KU-0059436 monotherapy:

- It is recommended patients are assessed weekly for their first cycle of monotherapy KU-0059436, with assessments as defined in the schedule of assessments for "Cycle 2 onwards Day 1, Day 8, Day 15, Day 21" (Table 10).

- Thereafter, it is recommended that safety assessments are performed every 6 weeks, as per the "Cycle 2 onwards Day 1" visit schedule (Table 10).

- During all the above visits no CRF data will be collected, however patients will be reviewed for SAEs and SAEs will be reported to Theradex within 24hrs (as detailed in Section 9.7)

9.10 Visit Schedule for Patients on Monotherapy KU-0059436 (Randomised Dose Expansion Phase)

A patient may continue on monotherapy KU-0059436 (tablet or capsule) if in the investigator's opinion they are deriving clinical benefit from KU-0059436 treatment and have to stop carboplatin/paclitaxel treatment because they have completed the prescribed course (minimum of 4 cycles) or due to toxicity.

Prior to receiving KU-0059436 monotherapy the tumour assessment at week 12 must be completed (unless otherwise agreed with AstraZeneca).

At the discretion of the PI and in consultation with AstraZeneca, the patient may receive up to the optimal recommended monotherapy dose, however once a dose is selected patients may not escalate the KU-0059436 again.

When patients initiate KU-0059436 monotherapy:

- It is recommended patients are assessed weekly for their first cycle of monotherapy KU-0059436, with assessments as defined in the schedule of assessments for '1st cycle of monotherapy' Day 1, Day 8, Day 15, Day 21" (Table 13).

- Thereafter, assessments should be performed, as per the '6 weekly' visit schedule (Table 13) for at least a further 12 weeks or until the data cut-off date, whichever is the later.

During the above visits, CRF data will be collected until the data cut-off, after which the clinical database will close to new data. After the data cut-off assessment information should still be collected in the patient's notes. Patients should attend visits according to routine clinical practice, but at least every 6 weeks until they meet any discontinuation criteria as per Section 7.14

SAEs will continue to be reported to Theradex within 24hrs for any patients that

continue on KU-0059436 until 30 days after study treatment is discontinued in accordance with section 9.6. Additionally as stated in Section 11.4.6 (Handling Unresolved Adverse Events/Serious Adverse Events at Withdrawal/Completion), any SAE or non-serious adverse event, that is ongoing at the end of the study, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

Table 9: Schedule of Study Evaluations for Dose Escalation Parts I and IIa

	Screening/ Baseline	Cycle 1 day							Cycle 2 onwards Day[21]				Withdrawal/ Final visit	Post 6 cycles visits per protocol/local clinical practice during treatment[19]	Follow-up post 30 days
		1	4[1]	8	9/ 10[17]	15	22	28[18]	1	8	15	21[18]			
Eligibility criteria	x	x*													
Medical history[2]	x	x*													
Physical exam[3]	x	x*							x				x		x
ECOG Performance Status	x	x*							x				x		
Adverse events	x	x		x		x	x	x	x	x	x	x	x		x
Con. Meds	x	x		x		x	x	x	x	x	x	x	x		
Vital Signs[4]	x	x		x		x	x	x	x	x	x	x	x		
Haematology[5]	x	x*		x*		x	x	x	x*	x	x	x	x		x
Coagulation[6]	x	x*							x						
Chemistry[7]	x	x*		x*		x	x	x	x*				x		
Markers CA-153/CA-125	x	x*							x						
Urinalysis[8]	x	x*							x				x		
Tumour Evaluation[9]	x											x	x		
Pregnancy Test[10]	x	x*													
ECG	x	x*											x		
PK[11]			x	x	x										
Pharmacogenetics[12]	x	x*													
Biomarker[13]	x	x*										x			x
Creatinine clearance[14]	x								x						
GFR	x														
Chest X-ray	x	x*											x		
Dispense KU-0059436[15]		x							x					x	
Carboplatin / carboplatin and paclitaxel[16]				x					x					x	
Pt Medication Record[15]		x	x	x	x	x	x	x							
SAE reporting only[20]														x	x

Comments to the flow chart:

1. Day 4 is only required for the dose escalation phase of the study.
2. Includes at baseline the history of the neoplastic disease, its previous therapy, pre-existing diseases and current medication.
3. Includes at baseline height, weight & body surface area, and during study a description of external signs of the neoplastic disease and weight.
4. Includes heart rate, blood pressure, respiratory rate and temperature. Includes weight on day 8 of cycle 1 and day 1 of each subsequent cycle and on withdrawal.
5. Hb, Hct, MCV, leukocyte count, differentials, absolute neutrophil and lymphocyte count, platelets. Samples taken within 3 days of day 1 for any cycle do not need to be repeated on day 1 prior to dosing.
6. INR and APTT should be performed monthly except where patient is receiving warfarin where assessments should be done weekly.
7. Sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]). Samples taken within 3 days of day 1 for any cycle do not need to be repeated on day 1 prior to dosing.
8. Dipstick for albumin, glucose, bilirubin and blood (microscopy if more than one positive test).
9. Radiographic or clinical assessment (see section 10.4). Baseline measurement to be performed within 4 weeks prior to treatment and then every 2 cycles until week 24 then every 12 weeks until confirmed progressive disease.
10. Female patients with reproductive potential. Urine or serum sample.
11. PK samples: See protocol section 10.1. PK samples are not required after cycle 1. Dose escalation phase only: PK samples will be taken on day 4 and day 8 (pre-dose and up to 8 hours post-dose).
12. Pharmacogenetic sample (9ml) to be collected either during screening or on Day 1 (can be taken any time during the study).
13. Blood and urine samples for potential retrospective analysis of biomarkers, collect pre dose, end cycle 2 and at follow up visit.
14. Creatinine clearance should be calculated using the Jaffe or enzymatic serum creatinine method close as possible but no more than 7 days prior to dosing with carboplatin.
15. Capsules may be dispensed on day 1 of each cycle or weekly if convenient to the patient/centre. The Patient Medication Record must be completed with the exact times on each day of KU-0059436 administration on PK sampling days.
16. Carboplatin or paclitaxel and carboplatin will be administered on day 8 of cycle 1 and day 1 of all other cycles, paclitaxel at least 1 hour after KU-0059436 capsules taken and carboplatin after 3 hour paclitaxel infusion.
17. Dose escalation phase only: Carboplatin and paclitaxel PK samples will be taken on days 8 and 9 (day 10 carboplatin only) during the dose escalation phase.
18. Except tumour evaluations and biomarker samples, visit evaluations will occur only if treatment delay or withdrawal, otherwise the patient will have evaluations as detailed in the next cycle day 1 visit.
19. After 6 cycles treatment or approval of protocol amendment 6, whichever occurs last, patients may continue on KU-0059436 and chemotherapy treatment as long as they are deriving clinical benefit in the opinion of the investigator and are tolerating the treatment without dose-limiting toxicities. Whilst on treatment patients will then be monitored in line with the clinical protocol, or as defined by local clinical practice. All SAEs will be reported to Theradex within 24 hours of becoming aware of the event.
20. For patients remaining on study following 6 cycles of treatment or after approval of protocol amendment 6, or if they have withdrawn prior to cycle 6 at 30 days after the last dose of study drug, patients will be assessed for any SAEs or ongoing SAEs. Follow-up of SAEs should be pursued until either the event has returned to the baseline grade (for pre-existing conditions); or until: the SAE is determined to be chronic, a cause is identified, the patient starts another anti-cancer therapy, in the opinion of the investigator the condition is unlikely to resolve due to the patient's underlying disease or the patient is lost to follow-up.
21. Patients receiving benefit from treatment with KU-0059436 and carboplatin/paclitaxel can continue provided they are free from intolerable toxicity. In the event that carboplatin/paclitaxel is permanently discontinued, treatment with KU-0059436 alone may continue (refer to table 10).

Examinations marked with * need not be repeated if already performed within 3 days.

Table 10: Schedule of Study Evaluations for Dose Escalation Phase Part III, Part IV, patients continuing on monotherapy KU-0059436 and Non- Randomised Dose Expansion Phase

	Screening / baseline	Cycle 1 Day						Cycle 2 onwards Day[23]				Withdrawal/ Final visit	Clinical visits per routine practice during treatment[21]	Follow-up post 30 days
		1	2/3[16]	8	10-12	15	21[17]	1	8	15	21[17]			
Eligibility criteria	x	x*												
Medical history[1]	x	x*												
Physical exam[2]	x	x*						x				x		x
ECOG Performance Status	x	x*						x				x		
Adverse events	x	x		x		x	x	x	x	x	x	x		x
Con. Meds	x	x		x		x	x	x	x	x	x	x		
Vital Signs[3]	x	x		x		x	x	x	x	x	x	x		
Haematology[4]	x	x*		x		x	x	x*	x	x	x	x		x
Coagulation[5]	x	x*						x						
Chemistry[6]	x	x*		x		x		x	x	x		x		
Markers CA-153/CA-125	x	x*						x						
Urinalysis[7]	x	x*						x				x		
Tumour Evaluation[8]	x										x	x		
Pregnancy Test[9]	x	x*												
ECG	x	x*										x		
PK[10,20]		x	x	x										
Pharmacogenetics[11]	x	x*												
Biomarker[12]	x	x*									x			x
PD samples[18, 20]		x	x	x	x	x		x[19]						
Creatinine clearance[13]	x							x						
GFR	x													
Chest X-ray	x	x*										x		
Dispense KU-0059436[14]		x						x					x	
Carboplatin and paclitaxel[15]		x						x					x	
Pt Medication Record		x	x	x										

SAE reporting only[22]													x	x

Comments to the flow chart:

1. Includes at baseline the history of the neoplastic disease, its previous therapy, pre-existing diseases and current medication.
2. Includes at baseline height, weight & body surface area, and during study a description of external signs of the neoplastic disease and weight.
3. Includes heart rate, blood pressure, respiratory rate and temperature. Includes weight on day 8 of cycle 1 and day 1 of each subsequent cycle and on withdrawal.
4. Hb, Hct, MCV, leukocyte count, differentials, absolute neutrophil and lymphocyte count, platelets. Samples taken within 3 days of day 1 for any cycle do not need to be repeated on day 1 prior to dosing.
5. INR and APTT should be performed monthly except where patient is receiving warfarin where assessments should be done weekly.
6. Sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]). Samples taken within 3 days of day 1 for any cycle do not need to be repeated on day 1 prior to dosing.
7. Dipstick for albumin, glucose, bilirubin and blood (microscopy if more than one positive test).
8. Radiographic or clinical assessment (see section 10.4). Baseline measurement to be performed within 4 weeks prior to treatment and then every 2 cycles until week 24 then every 12 weeks until confirmed progressive disease.
9. Female patients with reproductive potential. Urine or serum sample.
10. PK samples: See protocol section 10.1. Part III Dose escalation phase only: PK samples are not required after cycle 1 or in Part IV.
11. Pharmacogenetic sample (9ml) to be collected either during screening or on day 1 (can be taken any time during the study).
12. Blood and urine samples for potential retrospective analysis of biomarkers, collect pre dose, end cycle 2 and at follow up visit.
13. Creatinine clearance should be calculated using the Jaffe or enzymatic serum creatinine method close as possible but no more than 7 days prior to dosing with carboplatin.
14. Capsules/tablets may be dispensed on day 1 of each cycle or weekly if convenient to the patient/centre**.** KU-0059436 will be taken for a specified number of days from 1-20 with a defined rest period until day 21. The Patient Medication Record must be completed with the exact times on each day of KU-0059436 administration on PK sampling days.
15. Paclitaxel and carboplatin will be administered on Day 1 of each cycle, paclitaxel at least 1 hour after KU-0059436 capsules/tablets taken (if applicable) and carboplatin after 3 hour paclitaxel infusion.
16. Dose escalation phase only: Carboplatin and paclitaxel PK samples will be taken on days 1 and 2 (day 3 carboplatin only).
17. Except tumour evaluations and biomarker samples, visit evaluations will occur only if treatment delay or withdrawal, otherwise the patient will have evaluations as detailed in the next cycle day 1 visit.
18. PD samples will be taken as detailed in section 10.2 in the escalation phase only of part III, PD samples will be taken as detailed in section 10.2 in the escalation phase only of part III, KU-0059436 pharmacodynamic sampling will not occur in part IV of the study, Additional PD samples will be taken if any patient has a Grade 2 or greater haematological toxicity leading to a dose delay as close as possible to the onset of the toxicity.
19. PD sample is only taken pre-KU-0059436 dose on cycle 2 D1
20. If dosing is extended to 8 days or beyond then extra PD/PK samples will be collected on Day 18 of cycle 1 and the day 2 and day 8 PD/PK samples will not be collected.
21. After 6 cycles treatment or approval of protocol amendment 6, whichever occurs last, patients may continue on KU-0059436 alone or in combination with carboplatin/paclitaxel treatment as long as they are deriving clinical benefit in the opinion of the investigator and are tolerating the treatment. Whilst on treatment patients will then be monitored in line with the clinical protocol or as defined by local clinical practice. All SAEs will be reported to Theradex within 24 hours of

becoming aware of the event.

22. For patients remaining on study following 6 cycles of treatment or after approval of protocol amendment 6, or if they have withdrawn prior to cycle 6 at 30 days after the last dose of study drug, patients will be assessed for any new SAEs or ongoing SAEs. Follow-up of SAEs should be pursued until either the event has returned to the baseline grade (for pre-existing conditions); or in the opinion of the investigator the condition is unlikely to resolve due to the patient's underlying disease or the patient is lost to follow-up
23. Patients receiving benefit from treatment with KU-0059436 and carboplatin/paclitaxel can continue on treatment provided they are free from intolerable toxicity. In the event that carboplatin/paclitaxel is permanently discontinued, treatment with KU-0059436 alone may continue. If carboplatin/paclitaxel is permanently discontinued, it is recommended patients are assessed according to the Cycle 2 onwards Day 1, Day 8, Day 15 Day 21 visit schedule for the first cycle of monotherapy KU-0059436 and thereafter every 6 weeks in line with the "Cycle 2 onwards - Day 1" visit schedule. All SAEs will be reported to Theradex within 24 hours of becoming aware of the event.

Examinations marked with * need not be repeated if already performed within 3 days.

Table 11: Schedule of Study Evaluations for Dose Escalation Part IIb

	Screening/ Baseline	Cycle 1 Day												Cycle 2 onwards Day[21]									Withdrawal/ Final visit	Clinic visits[19]	F/U post 30 days
		1	4	8[16]	9[16]	11	15	18	22	25	28	31	35[17]	1	4[18]	8	11[18]	15	18[18]	21	25[18]	28[17]			
Eligibility criteria	x	x*																							
Medical history[2]	x	x*																							
Physical exam[3]	x	x*												x									x		x
ECOG Performance Status	x	x*												x									x		
Adverse events	x	x		x			x		x		x		x	x*		x		x		x		x	x		x
Con. Meds	x	x		x			x		x		x		x	x*		x		x		x		x	x		
Vital Signs[4]	x	x		x			x		x		x		x	x		x		x		x		x	x		
Haematology[5]	x	x*	x	x		x	x	x	x	x	x	x	x	x*	x	x	x	x	x	x	x	x	x		x
Coagulation[6]	x	x*												x											
Chemistry[7]	x	x*	x	x		x	x	x	x	x	x	x	x	x*	x	x	x	x	x	x	x		x		
Markers CA-153/CA-125	x	x*												x											
Urinalysis[8]	x	x*												x									x		
Tumour Evaluation[9]	x																					x	x		
Pregnancy Test[10]	x	x*																							
ECG	x	x*																					x		
PK (KU-0059436)[11]			x	x																					
PK (Paclitaxel)[12]				x	x																				

Pharmacogenetics[13]	x	x*																							
Biomarker[14]	x	x*																				x			x
Chest X-ray	x	x*																					x	x	
Bone marrow biopsy[1]																									
Dispense KU-0059436[15]		x												x											
Paclitaxel[16]				x			x		x					x		x		x							
Pt Medication Record		x	x	x	x	x	x	x	x	x	x	x	x												
SAE reporting only[20]																								x	x

Comments to the flow chart:

1. If clinically indicated.
2. Includes at baseline the history of the neoplastic disease, its previous therapy, pre-existing diseases and current medication.
3. Includes at baseline height, weight & body surface area, and during study a description of external signs of the neoplastic disease and weight.
4. Includes heart rate, blood pressure, respiratory rate and temperature. Includes weight on day 8 of cycle 1 and day 1 of each subsequent cycle and on withdrawal.
5. Hb, Hct, MCV, leukocyte count, differentials, absolute neutrophil and lymphocyte count, platelets. Samples taken within 3 days of day 1 for any cycle do not need to be repeated on day 1 prior to dosing.
6. INR and APTT should be performed monthly except where patient is receiving warfarin where assessments should be done weekly.
7. Sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]). Samples taken within 3 days of day 1 for any cycle do not need to be repeated on day 1 prior to dosing.
8. Dipstick for albumin, glucose, bilirubin and blood (microscopy if more than one positive test).
9. Radiographic or clinical assessment (see section 10.4). Baseline measurement to be performed within 4 weeks prior to treatment and then every 2 cycles until week 24 then every 12 weeks until confirmed progressive disease.
10. Female patients with reproductive potential. Urine or serum sample.
11. PK samples: See protocol section 10.1. PK samples are not required after cycle 1. PK samples will be taken on day 4 and day 8 (pre-dose and up to 8 hours post-dose).
12. Paclitaxel PK samples will be taken on days 8 and 9.
13. Pharmacogenetic sample (9ml) to be collected either during screening or on Day 1 (can be taken any time during the study).
14. Blood and urine samples for potential retrospective analysis of biomarkers, collect pre dose, end cycle 2 and at follow up visit.
15. Capsules may be dispensed on day 1 of each cycle or weekly if convenient to the patient/centre. The Patient Medication Record must be completed with the exact times on each day of

KU-0059436 administration on PK sampling days.

16. Paclitaxel will be administered on days 8, 15, and 22 of cycle 1 and days 1, 8 and 15 of all other cycles at least 1 hour after KU-0059436 administration.
17. Except for tumour evaluations and biomarker samples, visit evaluations will occur only if treatment delay or withdrawal, otherwise the patient will have evaluations as detailed in the next cycle day 1 visit.
    Not applicable after cycle 2, unless clinically indicated.
18. After 6 cycles treatment or approval of protocol amendment 6, whichever occurs last, patients may continue on KU-0059436 and chemotherapy treatment as long as they are deriving clinical benefit in the opinion of the investigator and are tolerating the treatment. Whilst on treatment patients will then be monitored in line with the clinical protocol or as defined by local clinical practice. All SAEs will be reported to Theradex within 24 hours of becoming aware of the event.
19. For patients remaining on study following 6 cycles of treatment or after approval of protocol amendment 6, or if they have withdrawn prior to cycle 6 at 30 days after the last dose of study drug, patients will be assessed for any new SAEs or ongoing SAEs. Follow-up of SAEs should be pursued until either the event has returned to the baseline grade (for pre-existing conditions); or in the opinion of the investigator the condition is unlikely to resolve due to the patient's underlying disease or the patient is lost to follow-up.
20. Patients receiving benefit from treatment with KU-0059436 and paclitaxel can continue provided they are free from intolerable toxicity. In the event that paclitaxel is permanently discontinued, treatment with KU-0059436 alone may continue (refer to table 10)

Examinations marked with * need not be repeated if already performed within 3 days.

Table 12: Schedule of Study Evaluations for Randomised Dose Expansion Phase – Combination Treatment

	Screening / baseline	Cycle 1 Day				Cycle 2 onwards Day				Cycle 4 tumour assessm't [18,20]	Cycle 6 onwards Day [17, 20,]	Visits post Data-cut-off [21]	Withdrawal / Final Visit	Follow-up post 30 days
		1	8	15	21[17]	1	8	15	21[17]	Week 12	1			
Eligibility criteria	x	x*												
Medical history[1]	x	x*												
Physical exam[2]	x	x*				x					x		x	x
ECOG Performance Status	x	x*				x					x		x	
Adverse events	x	x	x	x	x	x	x	x	x		x		x	x
Nausea; Vomiting; Fatigue Questionnaires[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]					x[3]			
Con. Meds	x	x	x	x	x	x	x	x	x		x		x	
Vital Signs[4]	x	x	x	x	x	x	x	x	x		x		x	
Haematology[5]	x	x*	x	x	x	x*	x	x	x		x		x	x
Coagulation[6]	x	x*				x					x			
Chemistry[7]	x	x*	x	x		x	x	x			x		x	
TSH, B12, homocysteine and folate[8]	x	x*				x					x		x	
Markers CA-153/ CA-125	x	x*				x				x				
Urinalysis[9]	x	x*				x					x		x	
Tumour Evaluation[10]	x								x	x	x[10]		x	
Pregnancy Test[11]	x	x*												
ECG	x	x*											x	
Pharmacogenetics[12]	x	x*												
Biomarker[13]	x	x*							x					x
Creatinine clearance[14]	x					x								
GFR	x													

Randomise via Centralised Randomisation Centre		x												
Chest X-ray	x	x*											x	
Dispense KU-0059436[15, 22]		x				x					x	x	x	
Carboplatin and paclitaxel[16, 22]		x	x[23]		x[23]	x	x[23]	x[25]			x	x	x	
SAE reporting only[21]												x	x	x

Comments to the flow chart:

1. Includes at baseline the history of the neoplastic disease, its previous therapy, pre-existing diseases and current medication
2. Includes at baseline height, weight & body surface area, and during study a description of external signs of the neoplastic disease and weight.
3. Relevant Nausea/Vomiting/Fatigue questionnaires to be completed by the investigator, at any time after consent if the patient has an AE related to Nausea, Vomiting or Fatigue. Questionnaires to be completed in both combination and monotherapy phases of the randomised dose expansion phase.
4. Includes heart rate, blood pressure, respiratory rate and temperature. Includes weight on day 8 of cycle 1 and day 1 of each subsequent cycle and on withdrawal.
5. Hb, Hct, MCV, leukocyte count, differentials, absolute neutrophil and lymphocyte count, platelets. Samples taken within 3 days of day 1 for any cycle do not need to be repeated on day 1 prior to dosing.
6. INR and APTT should be performed monthly except where patient is receiving warfarin where assessments should be done weekly.
7. Sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]). Samples taken within 3 days of day 1 for any cycle do not need to be repeated on day 1 prior to dosing.
8. TSH, B12, homocysteine and folate should be performed at baseline and then on day 1 of every cycle. Samples taken within 3 days of day 1 for any cycle do not need to be repeated on day 1 prior to dosing
9. Dipstick for albumin, glucose, bilirubin and blood (microscopy if more than one positive test).
10. Radiographic or clinical assessment (see section 10.4). Baseline measurement to be performed within 4 weeks prior to treatment and then every 2 cycles (6 weeks) until week 24 then every 12 weeks until confirmed progressive disease.
11. Female patients with reproductive potential. Urine or serum sample.
12. Pharmacogenetic sample (9ml) to be collected either during screening or on day 1 (can be taken any time during the study).
13. Blood and urine samples for potential retrospective analysis of biomarkers, collect pre dose, end cycle 2 and at follow up visit (if the follow-up visit is prior to the DCO).
14. Creatinine clearance should be calculated using the Jaffe or enzymatic serum creatinine method close as possible but no more than 7 days prior to dosing with carboplatin.
15. Capsules/tablets may be dispensed on day 1 of each treatment cycle or weekly if convenient to the patient/centre**.** KU-0059436 will be taken for a specified number of days from 0-20 with a defined rest period until day 21 within each or specified treatment cycles.
16. Paclitaxel and carboplatin will be administered on Day 1 of each cycle, paclitaxel at least 1 hour after KU-0059436 capsules/tablets taken (if applicable) and carboplatin after 3 hour paclitaxel infusion.

17. Except tumour evaluations and biomarker samples, visit evaluations will occur only if treatment delay or withdrawal, otherwise the patient will have evaluations as detailed in the next cycle day 1 visit.
18. After the 12 week tumour assessment, patients may continue on KU-0059436 + chemotherapy treatment as long as they are deriving clinical benefit in the opinion of the investigator and are tolerating the treatment. In the event that carboplatin/paclitaxel is permanently discontinued, treatment with KU-0059436 alone may continue,
19. After 6 cycles of treatment patients may continue on KU-0059436 + chemotherapy treatment as long as they are deriving clinical benefit in the opinion of the investigator and are tolerating the treatment. In the event that carboplatin/paclitaxel is permanently discontinued, treatment with KU-0059436 alone may continue,
20. Patients remaining on KU-0059436 + chemotherapy should continue to have their assessments on day 1 of every cycle in line with the clinical protocol up to the data-cut-off (DCO) (see section 7.12)
21. For patients remaining on study after the data cut-off (see section 7.12) patients will be assessed for any new SAEs or ongoing SAEs. Follow-up of SAEs should be pursued until either the event has returned to the baseline grade (for pre-existing conditions); or in the opinion of the investigator the condition is unlikely to resolve due to the patient's underlying disease or the patient is lost to follow-up. All SAEs will be reported to Theradex within 24 hours of becoming aware of the event. Patients to attend visits according to routine clinical practice but at least every 6 weeks
22. If applicable
23. Only applies if carboplatin and paclitaxel infusion are on a weekly schedule

Examinations marked with * need not be repeated if already performed within 3 days.

Table 13 Recommended Schedule of Study Evaluations for Randomised Dose Expansion Phase Patients Moving to KU-0059436 Monotherapy after Combination Treatment

	1st 'Cycle' of Monotherapy[14]				6 weekly visits[14]	Visits post Data Cut-off[15]	Withdrawal /Final Visit	Follow-up visit post 30 days
	Day1	Day 8	Day 15	Day 21				
Physical Exam[1]	x				x		x	x
ECOG Performance Status	x				x		x	
Adverse Events	x	x	x	x	x		x	x
Nausea / Vomiting / Fatigue Questionnaires[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
Con-Meds	x	x	x	x	x		x	x
Vital Signs[3]	x	x	x	x	x		x	x
Haematology[4]	x	x	x	x	x		x	x
Coagulation[5]	x				x		x	x
Chemistry[6]	x	x	x		x		x	x
TSH, B12, homocysteine, folate[7]	x				x		x	x
Urinalysis[8]	x				x		x	x
Tumour Evaluation[9]					x[9]			

	1st 'Cycle' of Monotherapy[14]				6 weekly visits[14]	Visits post Data Cut-off[15]	Withdrawal /Final Visit	Follow-up visit post 30 days
ECG							x	
Pharmacokinetics[10]			x	x				
Biomarker[11]							x	
Dispense KU-0059436[12]	x				x	x		
SAE reporting only[13]						x	x	x

1 Includes a description of external signs and neoplastic disease and weight
2 Relevant Nausea / Vomiting/ Fatigue questionnaires to be completed by the investigator, at any time after consent if the patient reports an AE related to Nausea, Vomiting or Fatigue
3 Includes heart rate, blood pressure, respiratory rate and temperature. Includes weight on day 1 of each subsequent cycle and withdrawal
4 Hb, Hct, MCV, leukocyte count, differentials, absolute neutrophil and lymphocyte count, platelets. Samples taken within 3 days of day 1 for any cycle do not need repeating on day 1 prior to dosing.
5 INR and APTT should be performed monthly except where patient is receiving warfarin where assessments should be done weekly.
6 Sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea, total protein, albumin, serum amylase, serum lipase and lactic dehydrogenase [LDH]). Samples taken within 3 days of day 1 for any cycle do not need to be repeated on day 1 prior to dosing.
7 TSH, B12, homocysteine and folate should be performed at baseline and then on day 1 of every cycle. Samples taken within 3 days of day 1 for any cycle do not need to be repeated on day 1 prior to dosing
8 Dipstick for albumin, glucose, bilirubin and blood (microscopy if more than one positive test).
9 Radiographic or clinical assessment (see section 10.4). Baseline measurement to be performed within 4 weeks prior to treatment and then every 2 cycles (6 weeks) until week 24 then every 12 weeks until confirmed progressive disease.
10 **Patients on monotherapy only**: Pharmacokinetic samples to be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6,8,10 and 12 h post dose on days 15 and 21 of the 1st cycle of monotherapy. On day 15 the patient must have fasted prior to dosing with KU-0059436; on day 21, the dose of KU-0059436 should be given 30 minutes post the start of a standard meal (see section 10.1.1). Once the KU-0059436 dose on day 21 has been given, no more food should be consumed for a 2 hour period.
11 Blood and urine samples for retrospective analysis of biomarkers, collect at follow-up visit (if the follow-up is prior to data cut-off).
12 At each visit in the treatment period, KU-0059436 will be dispensed sufficient for an appropriate number of days/cycles of treatment, depending on the dose level
13 All SAEs will be reported to Theradex within 24 hours of becoming aware of the event..

14 Upon switching to monotherapy olaparib, it is recommended that patients are assessed weekly: Day 1, Day 8, Day 15 Day 21 visit schedule for the first cycle of monotherapy KU-0059436 and thereafter every 6 weeks visit schedule (see section 9.10) until the data cut-off (see section 7.12). All SAEs will be reported to Theradex within 24 hours of becoming aware of the event..

15 For patients remaining on study after the data cut-off (see section 7.12) patients will be assessed for any new SAEs or ongoing SAEs. Follow-up of SAEs should be pursued until either the event has returned to the baseline grade (for pre-existing conditions); or in the opinion of the investigator the condition is unlikely to resolve due to the patient's underlying disease or the patient is lost to follow-up. All SAEs will be reported to Theradex within 24 hours of becoming aware of the event. Patients to attend visits according to routine clinical practice but at least every 6 weeks

10.0 EFFICACY AND SAFETY EVALUATIONS

10.1 Pharmacokinetics

10.1.1 KU-0059436

Appropriate scheduled sampling of blood for the analysis of the concentration of KU-0059436 will allow the assessment of KU-0059436 pharmacokinetics in this combination schedule during the dose escalation phase. See Table 14, Table 15 and Table 16 for the schedule of PK sampling. Detailed pharmacokinetic analysis will be obtained in the study to determine distinct pharmacokinetic profiles for:

* KU-0059436 when dosed alone.
* KU-0059436 when administered shortly after a meal
* KU-0059436 when dosed in combination with carboplatin alone and with carboplatin and paclitaxel.
* KU-0059436 when dosed with paclitaxel alone.

To accommodate the requirements of PK sampling, cycle 1 in Parts I and IIa will be a 28 day cycle in which KU-0059436 will be administered twice daily for the first 7 days before carboplatin and/or paclitaxel is administered on day 8. Patients should be instructed not to take their capsules until told to do so by the centre staff on days 4 and 8, when KU-0059436 PK samples are required. The pharmacokinetic samples for KU-0059436 alone in Parts I, IIa and IIb (see Table 14), may be taken on days 5, 6 or 7 for clinic convenience providing that the patient has continued their twice daily capsules, on no account can this sampling be performed prior to Day 4.

The pharmacokinetic samples for KU-0059436 alone in the monotherapy part after the randomised dose escalation phase (see Table 18), should be taken during the first cycle of monotherapy on days 15 and 21.

Further details on the bioanalytical sampling procedures can be found in the Biological Sampling Manual.

Table 14: Pharmacokinetic Blood Collection Time Points

(Day 4, Cycle 1, dose escalation phase Parts I, IIa and IIb)

0	Predose
30min	30mins
1hr	1hr
2hrs	2hr
3hrs	3hrs
4hrs	4hrs
6hrs	6hrs
8hrs	8hrs

Table 15: KU-0059436 Pharmacokinetics: Inter-study sampling

(dose escalation phase Parts I, IIa and IIb)

Cycle 1	8	0	Predose
		30min	30mins
		1hr	1hr
		2hrs	2hr
		3hrs	3hrs
		4hrs	4hrs
		6hrs	6hrs
		8hrs	8hrs

In the dose escalation phase Part III, if KU-0059436 is administered from day 1 up to day 7, pharmacokinetic samples for KU-0059436 will only be taken on day 1, 2 and 8 of cycle 1 as shown in Table 16.

Table 16: KU-0059436 Pharmacokinetics: Inter-study sampling

(dose escalation phase Part III, KU-0059436 dosing up to day 8)

Cycle 1	1	0	Predose
		30min	30mins
		1hr	1hr
		2hrs	2hr
		3hrs	3hrs
		4hrs	4hrs
		6hrs	6hrs
		8hrs	8hrs
	2	0	Pre dose
	8		Any time (take at same time as day 8 PD sample)

If KU-0059436 administration is extended to 8 days or beyond, then KU-0059436 pharmacokinetic samples will be collected on Day 1 and 18 of cycle 1 and the day 2 and day 8 samples will not be collected (see Table 17 below).

Table 17: KU-0059436 Pharmacokinetics: Inter-study sampling

(dose escalation phase Part III KU-0059436 dosing beyond day 8)

Cycle 1	1	0	Predose
		30min	30mins
		1hr	1hr
		2hrs	2hr
		3hrs	3hrs
		4hrs	4hrs
		6hrs	6hrs
		8hrs	8hrs
	18		Any time (take at same time as day 18 PD sample)

KU-0059436 pharmacokinetic sampling will not occur in the non-randomised dose

expansion phase or part IV of the study.
Pharmacokinetic sampling will occur on Day 15 and 21 after a patient from the randomised dose expansion phase has moved from combination treatment (KU-0059436 + carboplatin/paclitaxel to KU-059436 monotherapy. Patients should swallow the medication (capsules or tablets) whole with a glass of water during the morning and evening (or in the morning for once daily dosing) at the same times every day. This is to ensure a dose interval of approximately 12 hours. On Day 15 when the patient is providing PK samples, the patient should have their dose of KU-0059436 at least 3 hours after eating a light meal and refrain from eating for at least 2 hours post dose. On Day 21, the dose of KU-0059436 should be given 30 minutes post the start of a standard meal*. Once the KU-0059436 dose on day 21 has been given, no more food should be consumed for a 2 hour period.

Samples will be collected at the following timepoints (see Table 18 below)

Table 18: KU-0059436 Pharmacokinetics: Inter-study sampling

(Randomised Dose Escalation Phase – 1st cycle of KU-0059436 Monotherapy dosing)

15 – Normal fasting dosing (ie light meal taken 3 hrs prior to dosing)	0	Predose
	15 min	0.25h
	30 mins	0.5h
	1hr	1hr
	1hr 30 mins	1.5hrs
	2hrs	2hrs
	3hrs	3hrs
	4hrs	4hrs
	6hrs	6 hrs
	8 hrs	8 hrs
	10 hrs	10 hrs
	12 hrs	12hrs
21 – Dose to be administered within 30 mins of start of 'standard meal'*	0	Predose
	15 min	0.25h
	30 mins	0.5h
	1hr	1hr
	1hr 30 mins	1.5hrs
	2hrs	2hrs
	3hrs	3hrs
	4hrs	4hrs
	6hrs	6 hrs
	8 hrs	8 hrs
	10 hrs	10 hrs
	12 hrs	12hrs

*Standard meal: "a light breakfast" ie; a bowl of cereal, couple of slices of toast and a cup of tea.

10.1.2 Carboplatin

Samples of blood for the analysis of total platinum will be taken to allow the estimation of the area under the free carboplatin plasma concentration versus time curve. In the escalation phase Parts I and IIa the samples will be taken during cycle 1 day 8 pre-dose up 12hrs post carboplatin infusion and at 24 and 48 hours post infusion (see Table 19Table 19).

Table 19: Carboplatin Pharmacokinetics: Inter-study sampling schedule (dose escalation Parts I and IIa)

Cycle 1	8	0	Prior to administration
	8	0	End of infusion EOI
			EOI + 15 mins
			EOI + 30 mins
			EOI + 60 mins
			EOI + 2hrs
			EOI + 4 hrs
			EOI + 8hrs
			EOI+ 12 hrs
	9		EOI+ 24 hrs
	10		EOI+ 48 hrs

In the dose escalation phase Part III and IV, pharmacokinetic samples for carboplatin will not be performed.

10.1.3 Paclitaxel

Pharmacokinetic sampling for paclitaxel in dose escalation phase Parts IIa and IIb will be taken during cycle 1 on days 8 and 9 at the following time points (see Table 20).

Table 20: Paclitaxel Pharmacokinetics: sampling schedule

Cycle 1	8	0	Prior to administration
	8	0	1hr after start of infusion
			End of Infusion EOI
			EOI+ 6 hrs
	9		EOI+ 24 hrs

Pharmacokinetic sampling for paclitaxel in dose escalation phase Part III and IV will not be performed.

10.1.4 Randomised and Non-Randomised Dose Expansion Phases

PK samples for KU-0059436, carboplatin or paclitaxel will not be taken in the non-randomised dose expansion phase.

PK samples for KU-0059436 are planned to be taken in patients who move to monotherapy following the randomised dose expansion phase.

10.2 Pharmacodynamics

All patients in Part III after the date of this amendment, will participate in pharmacodynamic studies with serial blood sampling (PBMC) for protein, mRNA and biological evaluation of down stream effects of PARP inhibition such as PAR formation, microscopy for analysis of formation of RAD51 foci, DNA damage, (e.g. comet), DNA repair etc. In Part IV of the study, no pharmacodynamic sampling will be performed.

10.2.1 Dose escalation phase

In the dose escalation phase Part III, if KU-0059436 (including Melt-Extrusion (tablet) formulation) is administered from day 1 up to day 7, pharmacodynamic samples will be taken on days 1, 2, 8, 10-12 and 15 of cycle 1 and on day 1 of cycle 2 (see Table 21 below).

Table 21: Part III Pharmacodynamic: sampling schedule

(dosing up to 8 days)

Cycle 1	1	0	Prior to KU-0059436 dose
	1	2	2hr after KU-0059436 dose
	1	4	4hr after KU-0059436 dose
	2		Prior to KU-0059436 dose
	8		Any time (take at same time as day 8 PK sample
	10-12		Any time between days 10-12
	15		Any time
Cycle 2	1	0	Prior to **KU-0059436 dose**

If KU-0059436 (including Melt-Extrusion (tablet) formulation) administration is extended to 8 days or beyond then pharmacodynamic samples will be collected on days 1, 10-12, 15 and 18 of cycle 1 and the day 2 and day 8 pharmacodynamic samples will not be collected (see Table 22 below). One sample will also be taken on day 1 of cycle 2.

Table 22: Part III Pharmacodynamic: sampling schedule

(dosing beyond 8 days)

Cycle 1	1	0	Prior to KU-0059436 dose
	1	2	2hr after KU-0059436 dose
	1	4	4hr after KU-0059436 dose
	10-12		Any time between days 10-12
	15		Any time
	18		Any time (take at same time as day 18 PK sample
Cycle 2	1	0	Prior to **KU-0059436 dose**

In addition, if a CTCAE grade 2 or greater haematological toxicity that leads to a dose delay is noted, then an additional PBMC sample will be taken as close as possible to the day of onset of the haematological toxicity.

10.2.2 Dose expansion phase

No pharmacodynamic samples will be taken in the expansion phase of the study.

10.3 Biomarkers and Pharmacogenetics

Patients will provide samples for exploratory biomarker research at each of the visits referenced in the study flow chart subject to giving the appropriate consent. The CRF will capture date and time of sample acquisition and time of freezing where relevant. Patients will not be excluded from the study if these samples are not collected/made available. All analyses will be performed by an approved laboratory.

10.3.1 Tumour tissue samples for biomarker analysis

If available, an adequately sized (minimum of 2 mm x 2 mm) historical tumour tissue paraffin block from resection or a core biopsy from the primary tumour should be provided. This must have been taken at or since the time of diagnosis but prior to study entry. Alternatively, slides prepared from the block can be provided.

If possible, tumour cells from peritoneal lavage or ascitic fluid drainage may be obtained during the study. There are no specific time points for collection. Sample timings are at the investigator's discretion and if deemed clinically appropriate.

Analyses of samples may include:

PARP-1 inhibition; BRCA pathway dysfunction.

Pharmacodynamic markers such as PAR, phosphorylated Nijmegen breakage syndrome 1 protein (phospho-NBS1) and phospho-Histone H2AX.
Other biomarkers such as markers of DNA damage response, apoptosis and proliferation.

10.3.2 Blood samples for biomarker analysis

In Parts I, IIa, IIb, III and IV blood samples will be collected pre dosing, day 21 of cycle 2 and at the follow-up visit. These samples will be stored for possible retrospective exploratory biomarker research.

10.3.3 Urine samples for biomarker analysis

In Parts I, IIa, IIb, III and IV urine samples will be collected pre-dosing, day 21 of cycle 2 and at follow up visit. These samples will be stored for possible retrospective exploratory biomarker research.

10.3.4 Pharmacogenetics samples

Providing appropriate consent has been obtained, patients will be requested to provide

a blood sample (9ml) to be stored frozen at –80^{o}C for DNA extraction and potential pharmacogenetic analysis. Any genotyping performed will relate to the absorption, distribution, metabolism elimination or mode of action of KU-0059436 and any comparators, its related pathway and other oncogenic pathways.

10.4 Assessment of Anti-Neoplastic Activity

CT or MRI Scans (RECIST)

Tumour assessments should be performed at base-line (within 28 days before first dose of KU-0059436 [day 1, cycle 1]) and at the end of every two cycles. Tumour assessments will occur according to the study planned assessments up to and including the withdrawal visit.

Except for the randomised dose expansion phase, after 6 cycles treatment or approval of protocol amendment 6, whichever occurs last, patients will be monitored according to routine clinical practice with respect to their disease status.

Patients in the randomised dose expansion phase, will have their tumour assessments performed at baseline (within 28 days before first dose of KU-0059436 [Day 1 Cycle1] and at the end of every two cycles (6 weeks) until week 24 and then every 12 weeks until objective disease progression. Patients will continue to have their tumour assessments (as per the study plan) when moving to monotherapy KU-0059436 until objective disease progression.

Baseline contrast enhanced CT of the chest, abdomen and pelvis should be performed for the assessment of measurable lesions. Where iodine contrast is contra-indicated then contrast enhanced MRI of the abdomen and pelvis is preferred and non contrast enhanced CT of the chest is preferred to contrast enhanced MRI of the chest, pelvis and abdomen. Other regions should be scanned at base-line and followed-up where clinically indicated for the assessment of disease.

Localised post-radiation changes may occur and measurable lesions that have been previously irradiated will not be selected as target lesions, unless no other suitable lesions are available. Measurable lesions that have been irradiated less than 12 weeks prior to the date of registration will not be assessed as target lesions.

Non-target disease may also be assessed using clinical examination for superficial and palpable lesions.

Bone scanning will not be used as part of this protocol to assess bone lesions. Bone lesions may be followed by CT, MRI or x-ray as non-target lesions. Bone lesions which become symptomatic or new bone lesions present on bone scan performed at the investigator's discretion during the study and not followed as non-target lesions by CT, MRI or x-ray, will require a confirmatory CT, MRI or x-ray and will be recorded as new lesions.

Subsequent, repeat imaging should follow RECIST guidelines which require that the same method of assessment and the same technique be used to characterise each identified and reported lesion at baseline and during follow-up.

Unequivocal malignant disease identified on additional anatomical imaging, e.g. CT or MRI or bone scan confirmed by x-ray, CT, or MRI, prompted by symptoms at follow-up, is considered disease progression and should be recorded as new lesions.

Patients with measurable disease will have objective response assessment according

to RECIST (Appendix II). Measurable disease in this study is defined as:

Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (MRI or CT) or as ≥ 10 mm with spiral CT scan.

Responses (partial and complete responses [PR and CR respectively]) must be confirmed ≥ 4 weeks later. It should be noted that pre-clinical models indicate that there may be an initial delay in tumour response (i.e. an initial response of progressive disease [PD]), after which response is observed. This delay may occur at the time of the first scan. Therefore minimal progression at this time point is not unexpected. It is therefore important to confirm disease progression. At the discretion of the investigator, and if the patient is willing, any patient showing PD at week 8 may be given the option to continue for a further 4 weeks in order to confirm whether the patient definitely has PD, or whether the patient has improved to SD or better (i.e. the initial response of PD at week 8 was a delay in tumour response, as described above).

For the purposes of analysis AstraZeneca will determine visit and overall response using Investigator measurements of target lesions, assessment of non target lesions and new lesions collected on the CRF to derive the visit, best overall response, and other protocol endpoints using these data.

Response will be assigned as CR, PR, SD or PD at each scheduled imaging visit by the investigator.

Patients with non measurable disease only at base-line will be assessed for non target lesions and new lesions according to RECIST criteria (Appendix II).

For the purposes of analysis AstraZeneca will use the investigator measurements of target lesions, assessment of non target lesions and new lesions collected on the CRF to derive the visit, best overall response, and other protocol endpoints using these data.

10.5 Clinical endpoints

Objective response rate:

Objective response rate will be derived for patients with measurable disease at base-line. Patients' tumours will be assessed at the end of every 2 cycles. Outcome of each assessment will be categorized as CR, PR, SD or PD at each visit. Objective response will be defined as a best overall response of confirmed CR or PR. An overall best outcome will be derived based on the outcomes seen in the study.

Progression free survival:

For patients with measurable disease, disease progression will be based on RECIST criteria and for patients with non measurable disease on assessment of non target and new lesions as for RECIST. Death in absence of disease progression will be counted as disease progression. Progression Free Survival is defined as time from first treatment to time to documented progression. Patients who have not progressed at the time of analysis will be censored using the last available assessment date.

11.0 CLINICAL EVALUATION AND SAFETY

11.1 Adverse events (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. tachycardia, enlarged liver), an abnormal laboratory finding, symptom (e.g. nausea), or disease temporally associated with the use of study treatment, whether or not related to the study treatment.

AEs include the following:

- All suspected adverse medication reactions,
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a pre-existing illness.
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate AEs.
- Abnormalities in physiological testing or physical examination findings requiring clinical intervention or further investigation (beyond ordering a repeat, confirmatory, test).
- Laboratory abnormalities requiring clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (e.g. elevated liver enzymes in a patient with jaundice), should be described in the comments of the report of the clinical event rather than listed as a separate AE.

11.2 Definition of Serious Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening (i.e. the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe),
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity,
- Results in permanent impairment of function or permanent damage to a body structure, or requires intervention to prevent permanent impairment or damage,
- Is a new cancer,
- Is a congenital abnormality/birth defect,
- Is another medically important condition (i.e. one which may not be immediately life-threatening or result in death or hospitalisation, but is clearly of major clinical significance. It may jeopardise the patient, or may require intervention to prevent one of the other serious outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic

bronchospasm; blood dyscrasias or convulsions that do not result in inpatient hospitalisations; or development of drug dependency or drug abuse).

11.3 Study-Specific Considerations Regarding Definition of AEs/SAEs

11.3.1 Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the type of cancer for which the study drugs are being studied. It may be an increase in the severity of the cancer or an increase in the symptoms of the cancer. Expected progression of the patient's cancer and/or expected progression of signs and symptoms of the cancer, unless more severe in intensity or more frequent than expected for the patient's condition, should not be reported as an AE. Any events that are unequivocally due to progression of disease must not be reported as an AE.

The development of new metastases, or progression of existing metastases to the primary cancer under study, should be considered as disease progression and not an AE. Signs and symptoms clearly associated with metastases present at study entry should not be reported as AEs unless they are newly emergent (i.e. not previously observed in the patient), judged by the investigator to be unusually severe or accelerated, or if the investigator considers deterioration of disease related signs and symptoms to be caused directly by the IMPs.

11.3.2 Lack of Efficacy

When there is deterioration in the condition for which the study treatment is being used (e.g. ovarian and breast cancer), there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless AstraZeneca or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

11.3.3 Deaths

All deaths that occur during the study or within the protocol defined follow-up period after the administration of the last dose of study treatment (whichever was administered last), must be reported as follows:

Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the CRF but should not be reported as an SAE.

Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within 24 hours (see Section 11.4. for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death CRF'.

Deaths with an unknown cause should always be reported as a SAE. A post-mortem

maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to the Theradex Medical Advisor / AstraZeneca for reporting to the Sponsor's Drug Safety Department within the usual timeframes.

11.3.4 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 11.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.5 Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 11.4, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

11.3.6 Pregnancy

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 11.4. Pregnancy in itself is not regarded as an AE unless there is a suspicion that the study drugs may have interfered with the effectiveness of a contraceptive medication.

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE. Also, a spontaneous abortion is always considered to be a SAE and will be reported as described in Section 11.4.4.

In the event of pregnancy, which must be confirmed by a positive serum test, the investigator will collect pregnancy information on any patient who becomes pregnant whilst participating in this study, even when the pregnancy first becomes known when the patient is off study. The Investigator will record pregnancy information on the appropriate form and submit it to the appropriate AstraZeneca representatives within 2 weeks of learning of a patient's pregnancy. The patient will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the AstraZeneca representatives. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

11.4 Reporting of Adverse Events and Serious Adverse Events

All AEs, as defined in Section 11.1, encountered during the clinical study as well as any SAEs (defined in Section 11.2) will be reported in the appropriate section of the CRF. It is important that this includes the duration of the AE (onset/resolution dates), the severity, the relationship to the individual study drug and any concomitant

treatment dispensed (or other action taken).

For patients permitted to continue to receive KU-0059436 alone or in combination with carboplatin / paclitaxel beyond the closure of the clinical study database, Investigators will continue to report all SAEs to the sponsor's representative Theradex until 30 days after KU-0059436 treatment is discontinued.

Additionally any SAE that is ongoing at the time of the closure of the clinical study database and any new SAEs that arise subsequently must be followed up to resolution unless the event is considered by the investigator to unlikely resolve due to the underlying medical condition or the patient is lost to follow-up.

Those patients not enrolled in the dose randomisation phase and are continuing on monotherapy treatment at the 'final visit' should attend visits according to routine clinical practice but at least every 6 weeks until they meet the discontinuation criteria (section 7.14).

Patients enrolled in the dose randomisation phase and continuing on monotherapy at the data cut-off (see section 7.12) should attend visits according to the protocol defined visit schedule (see Table 12) but at least every 6 weeks until they meet the discontinuation criteria (section 7.14).

Patients continuing on study therapy (KU-0059436 and/or chemotherapy) will continue to be monitored in line with the protocol defined visit schedule or according to local clinical practice and during these visits patients will be reviewed for SAEs (section 9.6). Those patients continuing on monotherapy KU-0059436 will be monitored as detailed in sections 9.7 and 9.8.

11.4.1 Method for detecting AEs / SAEs

At each visit the method of detecting AEs and SAEs in this study will be by the following:

Information volunteered by the patient, or carer,

Open-ended and non-leading verbal questioning of the patient at every visit such as the following: How are you feeling? Do you have any health problems? Have you had any (other) medical problems since your last visit?

Observation by the investigational team, other care providers or relatives.

11.4.2 Definition of Relationship of AEs to the IMP

The Investigator will also be asked to assess the possible relationship between the AE and the KU-0059436, and/or carboplatin and/or paclitaxel. For an AE to be a suspected drug-related event there should be at least a reasonable possibility of a causal relationship between the KU-0059436 and/or carboplatin and/or paclitaxel and the AE (see Appendix III for guidelines on interpretation of causality and bullet points below). Expectedness will be based on a review of the Investigator Brochure for KU-0059436 and the prescribing information for carboplatin and/or paclitaxel.

- Time course – temporal relationship to receiving drug,

- Consistency with known drug profile,
- Dechallenge experience – AE resolves after stopping drug,
- No alternative cause – AE cannot be explained by aetiology, underlying disease, etc.
- Rechallenge experience – AE reoccurs when drug reintroduced,
- Laboratory tests.
- The causality of AEs (i.e. their relationship to study treatment), will be assessed by the investigator(s) who in completing the relevant CRF must answer 'Yes' or 'No' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by any of the following-study medication-other medication?'.

For further guidance on the interpretation of the causality question see Appendix III of the protocol.

In addition to making a causality assessment with respect to the study treatment, the investigator should also consider whether study participation (i.e. protocol mandated procedures such as invasive tests, change to existing therapy), contributed to the occurrence of the event. SAEs considered related to study participation should be reported in the usual SAE timeframes to Theradex whether they occur pre-, during or post- the study treatment period.

11.4.3 Definition of Severity of AEs

The severity of any AE will be graded according to the National Cancer Institute Common Terminology Toxicity Criteria for Adverse Events (NCI-CTCAE, version 3), where applicable.

For each episode, the highest severity grade attained should be reported. If an AE occurs that is not listed in the NCI-CTCAE booklet, the investigator will evaluate its severity using the definitions in Table 23.

Table 23: Definition of Severity of Adverse Events

Mild	Grade 1 - Does not interfere with the patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	Grade 2 - Interferes to some extent with the patient's usual function (enough discomfort to interfere with usual activity [disturbing]).
Severe	Grade 3 - Interferes significantly with the patient's usual function (incapacity to work or to do usual activities [unacceptable]).
Life Threatening/disabling	Grade 4 - Results in risk of death, organ damage, or permanent disability (unacceptable).
Death	Grade 5 - Event has a fatal outcome.

Note the distinction between the seriousness and the intensity of an AE. **Severe** is a measure of intensity; thus, a **severe** event is not necessarily a **serious** event. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 11.2.

11.4.4 SAE Reporting Procedure

Appropriate AstraZeneca representatives must be informed of any SAE that occurs in the course of the study within 1 day (i.e. immediately but no later than the end of the next business day) of when he or she becomes aware of it.

The investigator must report all SAEs, regardless of presumed causal relationship, to the Theradex Medical Advisor for the study who will check the information to ensure it is a valid case before forwarding the completed SAE form to AstraZeneca's patient safety department, by fax (or e-mail where a dedicated Patient Safety e-mail address is available).

Information on SAEs for immediate reporting purposes to AstraZeneca's patient safety department will be recorded on a specific SAE reporting form. Blank copies are included in the study Investigator's File.

AstraZeneca's patient safety department will ensure that adverse events (AE's), serious adverse events (SAE's) and Suspected Unexpected Serious Adverse Reactions are reported to competent authorities in the European Union as per EU directive 2001/20/EC.

SAEs occurring in the European Union:

[redacted]
UK
[redacted]

[redacted]
UK

11.4.5 Follow-up of Adverse Events/Serious Adverse Events

After the initial AE / SAE report, the investigator is required to follow up proactively each patient and provide further information to Theradex on the patient's condition. During the study, all AEs / SAEs should be followed up to resolution, or until the condition stabilises, unless the event is considered by the investigator to be unlikely to resolve due to the patient's underlying disease, or the patient is lost to follow up. Follow up information on SAEs must be also reported by the investigator within the same timeframes.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to Theradex / AstraZeneca within 24 hours as described in Section 11.4.

For SAEs, follow-up reports (as many as required) should be completed and faxed/emailed following the same procedure above. A final report is required for SAEs once the condition is resolved or stabilised and no more information about the

event is expected. The final report should be completed and faxed/emailed following the same procedure above.

Those patients not enrolled in the dose randomisation phase and are continuing to receive KU-0059436 alone or in combination with carboplatin/paclitaxel after completion of the Final visit following 6 cycles of combination treatment or the approval of amendment 6 (whichever is last), AEs will cease to be reported and follow up of ongoing AEs will occur as per routine clinical practice. This follow up will be documented in the medical notes only and not the CRF. All SAEs occurring on KU-0059436 and/or paclitaxel/carboplatin or up to 30 days after stopping treatment will be reported by the investigator to Theradex within 24 hours of becoming aware of the event.

Those patients enrolled in the dose randomisation phase continuing to receive KU-0059436 alone or in combination with carboplatin/paclitaxel after the data cut-off (see section 7.12), AEs will cease to be reported and follow up of ongoing AEs will occur as per routine clinical practice. This follow up will be documented in the medical notes only and not the CRF. All SAEs occurring on KU-0059436 and/or paclitaxel/carboplatin or up to 30 days after stopping treatment will be reported by the investigator to Theradex within 24 hours of becoming aware of the event.

Additionally any SAE that is ongoing at the time of the closure of the clinical study database and any new SAEs that arise subsequently must be followed up to resolution unless the event is considered by the investigator to unlikely resolve due to the underlying medical condition or the patient is lost to follow-up. Patients continuing on study therapy (KU-0059436 and chemotherapy) will continue to be monitored in line with the protocol defined visit schedule or according to local clinical practice and during these visits patients will be reviewed for SAEs (section 9.6) those patients continuing on monotherapy KU-0059436 will be monitored according as detailed in section 9.7.

11.4.6 Handling Unresolved Adverse Events/Serious Adverse Events at Withdrawal/Completion

All AEs and SAEs must be followed until resolution; unless either the event has returned to the baseline grade, or the event is determined to be chronic, or until a cause is identified; or until the patient starts another type of anticancer therapy, or unless in the opinion of the investigator the condition is unlikely to resolve due to the patient's underlying disease or the patient is lost to follow-up. AstraZeneca reserve the right to ask for further information on any AE which may be considered of interest.

11.4.7 Reporting Serious Adverse Events to IRB/IEC

In addition to reporting the SAE to AstraZeneca/Theradex, the investigator must also comply with the applicable requirements related to the reporting of SAEs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) which approved the study. The investigator must promptly report all deaths to the IRB/IEC which approved the study.

AstraZeneca, or its designee, Theradex, will inform investigators of all serious

unexpected adverse drug experiences attributed to the use of the IMP which are reported to AstraZeneca by other investigators, or from clinical studies, which have safety implications. These SAEs should also be reported promptly to the IRB/IEC in compliance with the local regulations (CPMP Note for Guidance 3C614A). Copies of all correspondence relating to reporting of any SAEs to the IRB/IEC should be maintained in the Investigator's Files and provided to Theradex.

11.4.8 AE reporting period

For patients not enrolled in the dose randomisation phase. non-serious adverse events and SAEs will be collected from the time consent is given, up to completion of the day 28 visit after 6 cycles of treatment or the approval of amendment 6 (whichever is last) or for patients who have withdrawn up to the end of the 30 day follow-up period.

Patients who have been combination study treatment for over 6 cycles by the time of approval of protocol amendment 6 will have a final safety assessment as per the Final visit schedule which will be the last data point recorded for each patient for the purpose of the clinical study.

For those patients enrolled in the dose randomisation phase non-serious adverse events and SAEs will be collected from the time consent is given, through to the data cut-off (section 7.12)

The clinical data base will close to all new data after the data cut-off.

For patients permitted to continue to receive KU-0059436 alone or in combination with carboplatin / paclitaxel beyond the closure of the clinical study database, investigators will continue to report all SAEs to the sponsor's representative Theradex until 30 days after KU-0059436 and/or carboplatin treatment is discontinued.

Additionally any SAE that is ongoing at the time of the closure of the clinical study database and any new SAEs that arise subsequently must be followed up to resolution unless the event is considered by the investigator to unlikely resolve due to the underlying medical condition or the patient is lost to follow-up.

Patients continuing on study therapy (KU-0059436 alone or in combination with chemotherapy) will continue to be monitored in line with the protocol defined visit schedule or according to local clinical practice and during these visits patients will be reviewed for SAEs (sections 9.6, 9.7, 9.8, 9.9, 9.10) In addition any known untoward event occurring subsequent to the AE reporting period that the investigator assesses as possibly related to the study treatment(s) should also be reported as an AE.

12.0 DATA EVALUATION AND ANALYSIS

12.1 Data Collection

All study data must be recorded (black ink ballpoint pen) on the Case Report Forms (CRFs) provided by AstraZeneca. The data will be recorded as soon as possible after they are generated. All sections of each CRF must be completed and each page identified with the patient's assigned registration number. Only the Principal Investigator or authorised co-investigators can sign the CRFs for assurance of exactitude and completeness of each page.

An explanation for the omission of any required data should appear on the appropriate page. Any corrections to the CRF must be made in a way that does not obscure the original entry. The correct data must be inserted with the reason for the correction (if appropriate) and the change dated and initialled by the investigator or authorised designee.

12.2 Data Processing

The collected data will be computerised and entered into a master file with appropriate and documented proofreading.

12.3 Population and Type of Analyses

As patients may continue to receive study therapy after completion of 6 cycles, analysis of the data from the study will begin once all patients entered into the non-randomised and randomised dose expansion phases of the study have completed 12 weeks of treatment or have withdrawn and been followed up for a minimum of 30 days. The study is descriptive in nature and is designed to provide provisional results regarding anti-tumour activity in specific patient populations. The sample size is primarily based on clinical and regulatory considerations and has no formal statistical basis.

Descriptive statistics and data listings will be used to describe the study population, the observed anti-neoplastic response and the biologic response. Anti-neoplastic response for the different populations included in the non-randomised and randomised dose expansion phases of the study will be evaluated separately. In the randomised dose expansion phase, anti-neoplastic response will also be evaluated according to treatment arm. All reported symptoms and adverse events will be coded according to the MedDRA coding system and presented and summarized by dose. Crude incidence rates will be based on the maximum intensity CTC grade for each patient. All patients who receive any amount of KU-0059436 will be included in these analyses. 95% confidence intervals will be calculated where appropriate.

Pharmacokinetic parameters for KU-0059436 will be calculated using non-compartmental analyses using WinNonLin. The carboplatin and paclitaxel AUC will be calculated based on PK samples taken during the dose escalation phase.

12.4 Patient Follow-Up

For patients who withdraw prior to completion of 6 cycles of combination treatment a final Follow-up Visit should be conducted 30 days after the last dose of the study treatment(s). Any serious and/or non-serious AEs ongoing at the time of the Withdrawal Visit/ Final visit after 6 cycles of treatment or which have occurred since the last dose of study treatment(s) must be followed-up (in accordance with Section 11.4.6) and appropriate safety evaluations repeated and/or additional tests performed at any time when clinically indicated. If the patient is lost to follow up, then this should be noted in the CRF.

For all remaining patients permitted to remain on KU-0059436 alone or in combination with carboplatin / paclitaxel treatment after completion of the Final visit,

following 6 cycles of combination treatment or approval of amendment 6 (whichever is last), AEs will cease to be reported but documented in the medical notes. All new SAEs occurring on study treatment or up to 30 days after stopping treatment will be reported by the investigator to Theradex within 24 hours of becoming aware of the event. Additionally any SAE that is ongoing at the time of the closure of the study database and any new subsequent SAEs must be followed up until resolution unless the event is considered by the investigator to be unlikely to resolve due to the underlying medical condition or the patient is lost to follow-up.

12.5 Discontinuations

The patient record and the CRF should contain precise description of any discontinuation or withdrawal from the protocol treatment and a conclusion as to **one** of the following categories of underlying reasons:

- Adverse event
- Death (requires SAE report and notification to AstraZeneca.)
- Withdrawal of consent
- Protocol violation
- Lost to follow-up
- Disease Progression

Other reasons, (e.g. development in underlying neoplastic disease)**.**

13.0 STUDY MANAGEMENT AND QUALITY CONTROL

13.1 Ethical and Legal Considerations

The study will be conducted in accordance with the guidelines in Good Clinical Practice (ICH-GCP) and the World Medical Association's Declaration of Helsinki (Appendix I) and applicable regulatory requirements.

The study will not be initiated without approval of the appropriate Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and compliance with all administrative requirements of the governing body of the institution. This protocol, consent procedures, and any amendments must be approved by the IRB/IEC in compliance with current regulations as applicable and in accordance with ICH/GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IRB/IEC will be kept informed by the Chief Investigator, Theradex® or the Sponsor, as required by national regulations, as to the progress of the study as well as to any serious and unexpected adverse events.

Details of the IRB/IEC composition including names of their members, their qualifications and what function they perform on the committee, (e.g.: chairman, specialist, lay-member) will be made available to conform to regulations governing the conduct of clinical studies within the Netherlands and UK. If available, the constitution of the IRB/IEC must also be supplied.

13.2 Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current signed and dated curriculum vitae and a financial disclosure statement to Theradex®. All co-investigators will be required to provide a current curriculum vitae and a financial disclosure statement to Theradex®.

13.3 Patient Information and Informed Consent

The Principal Investigator at each centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time (at least 24 hours) to consider the information provided.

The patient's signed and dated informed consent (ICF) must be obtained before conducting any procedure specifically for the study. Although nursing staff may be involved in describing the study to a patient, the investigator must participate in discussions with the patient **and sign** and personally date the Informed Consent documentation. The signed and dated informed consent forms will be kept by the investigator and will be available for inspection by AstraZeneca and the authorities. A copy of the signed written Informed Consent Form must be given to the patient.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca and the IRB/IEC.

The ICF will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, and the ICH Guideline for Good Clinical Practice, Section 4.8.

The written informed consent form will explain that the study data will remain confidential in accordance with national data legislation. Initials and patient number only will identify patients in the database. The written Informed Consent Form will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, an IEC or IRB may require direct access to parts of the hospital records relevant to the study, including the patient's medical history.

The patient information and informed consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the patient. In this instance the IRB/IEC should always give approval; existing patients must be informed of the changes where relevant, and signed consent obtained for the new changes.

The investigator should, with the consent of the patient, inform the patient's primary physician about their participation in the clinical study.

As used in this protocol, the term "informed consent" includes all consent and/or assent given by patients, or their legal representatives.

13.4 Insurance and Indemnity

With respect to any liability directly or indirectly caused by the investigational products in connection with this Clinical Study, AstraZeneca assumes liability by law

on behalf of the investigator(s) and his assistants for possible injury to the patient provided the investigator(s) and his assistants have followed the instructions of AstraZeneca in accordance with this protocol and any amendments thereto, that the investigational products administered to the patient in this Clinical Study have been supplied by AstraZeneca and that the investigator and his assistants have performed this clinical study in accordance with scientific practice and currently acceptable techniques and know-how.

A letter of indemnity will be signed between AstraZeneca, and the Investigator(s)' institution, and AstraZeneca will insure all patients according to local requirements.

13.5 Monitoring

Before the study begins, a representative of AstraZeneca will visit the investigational site to determine the adequacy of the facilities and to discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives.

During the study, a monitor representing AstraZeneca will have regular contacts with the investigational site, including visits to:

- provide information and support to the investigators(s)
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the protocol
- confirm that data are being accurately recorded in the case report forms (CRFs)
- confirm that the study is conducted according to the guidelines for ICH/GCP
- confirm that an update of the screening log is performed, and that investigational product accountability checks are being performed
- perform source data verification (a comparison of the data in the CRFs with the patient's records at the hospital or practice, and other records relevant to the study).

This will require direct access to all original records for each patient (e.g., clinic charts).

The monitor or another AstraZeneca representative will be available between visits if the investigators(s) or other staffs at the centre need information and advice.

13.6 Audit

Authorised representatives of AstraZeneca and/or a national regulatory authority may visit the centre to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study related activities and documents. Such inspections will determine whether these activities were conducted, and data recorded, analysed, and accurately reported, according to the protocol, Good Clinical Practice (GCP)

guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigators should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at their centre.

13.7 Training of Staff

The Principal Investigator will maintain a record, "authorised representative signature sheet", of all individuals involved in the study (medical, nursing and other staff). In collaboration with AstraZeneca the investigator will ensure that appropriate training relevant to the study and/or study procedures, is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

13.8 Sponsorship, Filing and Data Management

AstraZeneca AB will be sponsoring the study. Patient data will be registered at the treatment centre. AstraZeneca or it representatives will supply the treatment centre with all necessary material and case report forms (CRF) at the initiation of the study. Each case report form and patient notes will be evaluated carefully by monitors representing AstraZeneca to ensure full protocol compliance with the planned procedures as regards data filing and follow-up. A project representative from AstraZeneca will be available for the treatment centres by telephone and/or by visit.

The investigator is responsible for filling in the CRF forms and including all relevant data. The CRF forms will be monitored by representatives of AstraZeneca who will contact the investigator should the need arise for further clarification. AstraZeneca will enter all the data into a validated and approved medical database. Data lists will be generated from the database enabling a direct comparison between the original case report forms and the database. This will facilitate the correction of any mistakes. These corrected documents, and other study documents, will be retained as the final study documentation, and be filed for at least 2 years after marketing approval ends, which is expected to be at least 15 years, in total.

The investigator must arrange for the retention of the patient identification codes (i.e. hospital/unit code, study identification code and study number) for as long as the sponsor requests after completion or discontinuation of the clinical study. Other source documents, such as patient files and clinic case notes, must be retained for the maximum period of time permitted by the hospital, institution or private practice and if this is less than the sponsor requires after the completion or discontinuation of the clinical study, then AstraZeneca must be notified to arrange record retention.

If the Principal Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintaining the study documentation, AstraZeneca must be notified (in writing) so that adequate provision can be made with regard to the patient identification codes, their copies of the study documentation (e.g. copies of the CRFs) and other source data (if available). This responsibility may be transferred to AstraZeneca who will make arrangements to store the data. An inventory of stored data will be held by the investigator with a copy of this inventory also being kept by AstraZeneca.

13.9 Financing of the Study

AstraZeneca will financially support this study. The company will deliver the study medication free of charge, as well as paying the investigator a fee for the patients included, which will cover the study costs. The costs for carboplatin and paclitaxel will be covered by AstraZeneca in the event that they are not covered through local insurance/reimbursement. No money will be paid to the patients other than any reasonable travel costs.

13.10 Reporting of the Study

A representative for AstraZeneca will perform the statistical analysis and will provide the investigators with a written report within 3-months of study completion. Investigators have access to all data related to the study in regards to the Uniform Requirements developed by International Committee of Medical Journals Editors (ICMJE).

The final clinical report of this study will be prepared by AstraZeneca and submitted to the investigators for comments and approval. The final report may also be submitted to relevant Health Authorities to support a request for registration.

13.11 Publication of the Study

The study results will be submitted for publication in a relevant medical journal with authorship according to requirements for manuscripts in the Vancouver Statements. All oral or written communications /publications concerning the study results will have to be reviewed and approved by AstraZeneca, who has a 30-day period to respond.

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APPENDIX 1: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI (2004 VERSION)

APPENDIX II: DEFINITIONS OF MEASURABLE, TARGET AND NON-TARGET LESIONS AND OBJECTIVE RESPONSE CRITERIA BASED ON THE RECIST CRITERIA USED IN THIS STUDY

Below are definitions of measurable, non-measurable, target and non-target lesions and objective response criteria based on the RECIST criteria to be used in this study.

DEFINITION OF MEASURABLE AND NON-MEASURABLE LESIONS

Measurable	Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan.
Non-measurable	All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly non-measurable lesions.

Lesions that are considered as truly non-measurable include the following:

- Bone lesions;
- Leptomeningeal disease;
- Ascites;
- Pleural / pericardial effusion;
- Inflammatory breast disease;
- Lymphangitis cutis/pulmonis;
- Abdominal masses that are not confirmed and followed by imaging techniques;
- Cystic lesions;
- Superficial and palpable lesions assessed by clinical examination or photography.

Note: Breast cancer patients can have curative and palliative external beam radiation treatment. Localised post-radiation changes may occur and measurable lesions that have not been previously irradiated will not be selected, unless no other suitable lesions are available. Lesions that have been irradiated less than 12 weeks prior to the date of enrolment will not be assessed as measurable lesions.

Methods of Measurement

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment.

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

Clinical lesions (non target / new lesions only)

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is

recommended.

Given that superficial and palpable lesions are difficult to measure these will be assessed as non target and new lesions for this study.

X-ray (confirmation of bone lesions only)
Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is the best method available and will be used in this study and chest x-ray will not be used to assess chest lesions.

Lesions identified on bone scan can be followed as non-target lesions using x-ray, CT or MRI or confirmed as new lesions using x-ray in addition to CT and MRI if they become symptomatic.

CT and MRI (used in this study to assess all lesions)
CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

CT and MRI will be used in this study to assess measurable target lesions and may be used to assess non-target and new lesions.

Ultrasound (not used in this study)
Ultrasound should not be used to measure tumour lesions for objective response evaluation. It is however a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Given the known issues with ultrasound for assessing tumour extent it will not be used in this study as part of the RECIST assessment.

Endoscopy and laparoscopy (not used in this study)
The utilisation of these techniques for objective tumour evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centres. Therefore, the utilisation of such techniques for objective tumour response should be restricted to validation purposes in reference centres. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

As these methods have not been validated for assessing objective response, they will not be used as part of the RECIST assessment in this study.

Tumour markers

Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalise for a patient to be considered in complete clinical response.

Tumour markers are not recognised as forming part of RECIST response assessment in breast and ovarian cancers and therefore will not be used in this study (however CA-153 and CA-125 will be collected for separate analysis).

Cytology and histology (not required for this study)

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). This is not applicable to breast cancer and will not be used for this study.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

In the absence of negative cytology findings for pleural effusion that worsens or appears, this will be considered to be disease progression due to new lesions or progression of non-target lesions.

TUMOUR RESPONSE EVALUATION

Assessment of overall tumour burden and measurable disease

To assess objective **response**, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included where measurable disease is defined by the presence of at least one measurable lesion.

If the measurable disease is restricted to a solitary lesion, its neoplastic nature may require confirmation by cytology/histology.

Documentation of "target" and "non-target" lesions

All measurable lesions up to a maximum of 10 lesions representative of all involved organs (maximum of 5 lesions per organ) should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the

baseline sum LD. The baseline sum LD will be used as reference to further characterise the objective tumour response of the measurable dimension of the disease.

The longest diameter will be measured and recorded for all target lesions identified at baseline at follow-up assessments and the sum LD calculated.

If a lesion splits into two or more parts, then the sum of the LDs of those parts is recorded.

If two or more lesions merge, then the LD of the combined lesion should be recorded for one of the lesions and zero recorded for the other lesion.

If a lesion becomes too small to measure, then the size below which measurement cannot be accurately obtained should be substituted for the LD and used in the sum LD.

If a lesion cannot be measured accurately due to it being too large, and was measurable previously, then the maximum measurable size should be recorded as the LD and should be used in the sum LD and response assessment.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent" or "present with progression".

RESPONSE CRITERIA

Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions.
Partial Response (PR)	At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.
Progressive Disease (PD)	At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

Note: Appearance of new lesions only counts towards the overall visit response, not towards the response of target or non-target lesions.

Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker level.
Incomplete Response / Stable Disease	Persistence of one or more non-target lesion or/and maintenance of tumour marker level above the normal limits.
Progression (PD)	Unequivocal progression of existing non-target lesions.

Note: Appearance of new lesions only counts towards the overall visit response, not towards the response of target or non-target lesions.

Evaluation of overall visit response and best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Best overall response will be derived as part of the study analysis by the sponsor.

Overall visit response will be derived by the investigator at site and recorded on the CRF. Overall visit response will be derived from assessment of target, non target and new lesions as part of the analysis for this study.

Target lesions	Non-target lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease.
See text for more details.

CONFIRMATORY MEASUREMENT

Confirmation

The main goal of confirmation of objective response is to minimise the risk of overestimation of the response rate. This aspect of response evaluation is particularly important in non-randomised studies where response is the primary endpoint. In this study responses (partial and complete responses [PR and CR respectively]) must be confirmed ≥ 4 weeks' later.

SPECIFICATIONS FOR RADIOLOGICAL IMAGING

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

CT

CT scans of the thorax, abdomen and pelvis should be contiguous throughout the anatomical region of interest.

The type of CT scanner is important regarding the slice thickness and minimum sized lesion.

For spiral (helical) CT scanners, the minimum size of any given lesion at baseline should be 10 mm and the images reconstructed contiguously at 5 mm intervals.

For conventional CT scanners, the minimum sized lesion should be 20 mm using a contiguous slice thickness of 10 mm.

For the other body parts, where CT scans examination are of different slice thickness e.g. neck, which are typically of 5 mm thickness, the minimum sized lesion allowable will be different.

In patients in whom the abdomen and pelvis have been imaged, oral contrast agents should be given to accentuate the bowel from other soft tissue masses.

Intra-venous (IV) contrast agents should also be given, unless contra-indicated for medical reasons, such as allergy. This is to accentuate vascular structures from adjacent lymph node masses and to help enhance liver and other visceral metastases.

The method of administration of IV contrast agents is variable. It is appropriate to suggest that an adequate volume of a suitable contrast agent should be given such that the metastases are better differentiated; a consistent method should be used on subsequent examinations for any given patient.

All window settings should be included, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the target lesions should be measured on the same window setting for repeated examinations throughout the study.

All images from each examination should be included and not "selected" images of the apparent lesion.

MRI

MRI is a complex issue. MRI is entirely acceptable and capable of providing images in different anatomical planes. It is important therefore that when it is used lesions must be measured in the same anatomical plane using the same imaging sequences on subsequent examinations. MRI scanners vary in the images produced. Wherever possible, the same scanner should be used.

Moreover many patients with advanced malignancy are in pain, so their ability to remain still for the duration of a scan sequence, in the order of 2-5 minutes is limited. Any movement during the scan time leads to motion artefacts, degradation of image quality such that the examination will probably be useless.

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

Note: Same method of examination
The same imaging modality must be used throughout the study to measure disease. Different imaging techniques have differing sensitivities, so any given lesion may have different dimensions at any given time if measured with different modalities.

It is therefore, not acceptable to interchange different modalities throughout a study and use these measurements. It must be the same technique throughout.

APPENDIX III: FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT AND INTERPRETING THE CAUSALITY QUESTION

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious. Simply stopping the suspect investigational medicinal product (IMP) does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

Angioedema not severe enough to require intubation but requiring i.v. hydrocortisone treatment,

Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine,

Intensive treatment in an emergency room or at home for allergic bronchospasm,

Blood dyscrasias (e.g. neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation,

Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

Rechallenge experience. Did the AE reoccur if the suspect IMP was reintroduced after having been stopped? Rechallenge is not normally recommended or supported.

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

A “reasonable possibility” could be considered to exist for an AE where one or more of these factors exist. In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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

Is this a recognised feature of overdose of the IMP?

Is there a known mechanism?

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

APPENDIX IV: ACCEPTABLE BIRTH CONTROL METHODS

KU-0059436 is regarded as a compound with medium/high foetal risk.

Patients of childbearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 12 weeks after last dose of study drug(s).

Acceptable non-hormonal birth control methods include

- Total sexual abstinence. Abstinence must be for the total duration of the trial and the drug washout period.
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal occlusion plus male condom with spermicide
- IUD plus male condom + spermicide. Provided coils are copper-banded

Acceptable hormonal methods

- Etonogestrel implants (e.g., Implanon, Norplan) + male condom with spermicide
- Normal and low dose combined oral pills + male condom with spermicide
- Norelgestromin / EE transdermal system + male condom with spermicide
- Intravaginal device + male condom with spermicide (e.g., EE and etonogestrel)
- Cerazette (desogestrel) + male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.