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CLINICAL STUDY PROTOCOL - CONFIDENTIAL

Study Title:	A Phase I, Open-Label, Study of the Safety and Tolerability of KU-0059436 in combination with Gemcitabine in the Treatment of Patients with Advanced Solid Tumours.
Protocol Number:	KU36-29
EudraCT:	2006-007000-42
IND number:	75,918
Contract Research Organisation (CRO)	[redacted]
Indication:	Escalation phase: Advanced solid tumours/advanced pancreatic cancer Expansion phase: Advanced pancreatic cancer
Development Phase:	Phase I
Sponsor:	[redacted]
Sponsor's Responsible Medical Officer:	[redacted]
Final protocol Amendment 1 dated: Amendment 2 dated: Amendment 3 dated:	[redacted]

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)

AstraZeneca

PROTOCOL APPROVAL SIGNATURES:

CLINICAL CENTRE: CHIEF/COORDINATING INVESTIGATOR

[redacted]

GENERAL INFORMATION

Study Role	Name	Address
[redacted]	[redacted]	[redacted]
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CLINICAL STUDY SYNOPSIS

Name of Sponsor: [redacted]	**Name of Monitor:** [redacted]
Name of finished product: KU-0059436	
Name of active ingredient: KU-0059436	
Title of the study: A Phase I, Open-Label, Study of the Safety and Tolerability of KU-0059436 in combination with Gemcitabine in the Treatment of Patients with Advanced Solid Tumours.	
Investigators and study centres: See Study Operations Manual	
Publication (reference): Not applicable	
Clinical phase: Phase I	

Objectives:

Primary Objective:

- To investigate the safety and tolerability and establish either the dose of KU-0059436 which is:
  - the Maximum Tolerated Dose (MTD) of KU-0059436 administered orally in combination with Gemcitabine to patients with advanced malignant solid tumours.

  Or if an MTD cannot be determined :

  - a tolerable and effective dose of KU-0059436 in combination with an active dose of Gemcitabine (in the opinion of the investigators and sponsor).

Secondary Objectives:

- To identify the Dose Limiting Toxicity (DLT) of the combination of KU-0059436 and Gemcitabine.
- To determine the plasma pharmacokinetic profile of KU-0059436 alone and in combination with Gemcitabine.
- To determine the plasma pharmacokinetic profile of Gemcitabine alone and in combination with KU-0059436.
- To enable a preliminary assessment of the anti-tumour activity of KU-0059436 when given in combination with Gemcitabine compared to Gemcitabine alone in terms of progression free survival (PFS), overall survival (OS) and maximum tumour reduction
- To determine the safety and tolerability profile of the KU-0059436 Melt-Extrusion [tablet] formulation in combination with Gemcitabine.
- To select a dose of KU-0059436 tablet and capsule in combination with Gemcitabine for further studies.

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.

Methodology:

This is an open-label, multi-centre, phase I study of KU-0059436 when administered orally in combination with Gemcitabine to patients with solid tumours in the dose escalation part and with advanced pancreatic cancer in the dose expansion part. The dose escalation part is to establish the MTD, or an effective dose of KU-0059436 (capsules) in combination with an active dose of Gemcitabine that can be administered safely. The dose-expansion part will test the selected combination dose compared to Gemcitabine alone and will further establish the safety and preliminary response data of the two treatment groups. The dose expansion part of the study will be randomised (2:1) between a combination of KU-0059436 (capsules) plus Gemcitabine versus Gemcitabine alone. The stratification for randomisation will be based on severity of disease, i.e., locally advanced or metastatic unresectable disease. Each cycle of treatment will last for four weeks. A maximum of 12 patients will be recruited into a separate dose escalation phase to determine a tolerable dose of KU-0059436 Melt-Extrusion [tablet] formulation in combination with Gemcitabine for future studies.

Number of patients: A maximum of 70 (escalation and expansion phase combined).

Diagnosis and main criteria for inclusion:

A maximum of 47 evaluable patients will be enrolled in the dose escalation part of the study and a maximum of 23 evaluable patients will be enrolled in the dose expansion part of the study.

1. Fully-informed written consent.
2. Dose escalation phase (capsule):
   Histologically or – where acceptable - cytologically confirmed malignant solid tumour refractory to standard therapy or for which no suitable effective standard therapy exists or for which Gemcitabine would be considered a potential treatment option.
   Dose escalation phase (tablet):
   a. Histologically or cytologically confirmed adenocarcinoma of the pancreas.
   b. Locally advanced or metastatic unresectable disease.
   Dose expansion phase (capsule):
   a. Histologically or cytologically confirmed adenocarcinoma of the pancreas.
   b. Locally advanced or metastatic unresectable disease.
3. Clinical or radiological evidence of disease. Measurable disease at baseline is only mandatory for the dose expansion part of the study (lesions that can be accurately measured in at least one dimension as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan).
4. Age ≥ 18 years.
5. Adequate bone marrow, hepatic (with stenting for any obstruction, if required) and renal function including the following:
   a. Haemoglobin ≥ 10.0 g/dl, absolute neutrophil count ≥ 1.5 x 10^9/L, platelets ≥100 x 10^9/L;
   b. Total bilirubin ≤ 1.25 x upper normal limit. For patients with advanced pancreatic cancer, total bilirubin ≤ 2.0 x upper normal limit;
   c. AST (SGOT), ALT (SGPT) ≤ 2.5 x upper normal limit;
   d. Creatinine ≤ 1.5 x upper normal limit.
6. Performance status (PS) ≤ 2 (ECOG scale).
7. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 1 day prior to start of trial.
8. 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.
9. Life expectancy of at least 12 weeks.

Exclusion Criteria:

1. Dose escalation phase (capsule):
   Any anti-cancer chemotherapy, radiotherapy (except for palliative reasons), endocrine- or immunotherapy or use of other investigational agents administered within four weeks prior to start of study treatment. 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 the event below:
   - Significant treatment delays in previous chemotherapy courses due to bone marrow toxicity

   Dose escalation phase (tablet):
   No prior anti-cancer chemotherapy, radiotherapy (excluding palliative radiotherapy administered more than 4 weeks prior to study entry), endocrine- or immunotherapy or use of other investigational agents.

   Dose expansion phase (capsule):
   No prior anti-cancer chemotherapy, radiotherapy (excluding palliative radiotherapy administered more than 4 weeks prior to study entry), endocrine- or immunotherapy or use of other investigational agents.
2. Major surgery within 4 weeks of starting the study and patients must have recovered from effects of major surgery.
3. Patients with active second primary cancer, except adequately treated basal skin cancer or carcinoma in-situ of the cervix.
4. Clinically significant cardiovascular disease as defined by one or more of the following:
   a. history of clinically significant congestive heart failure;
   b. history of unstable angina pectoris or myocardial infarction up to 6 months prior to trial entry;
   c. presence of severe valvular heart disease;
   d. presence of a ventricular arrhythmia requiring treatment.
5. Known rapidly deteriorating liver function (≥2 ULN rise in AST/ALT in the week preceding the study).
6. 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 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. Patients with known brain tumours or metastases will be excluded from this clinical trial if their disease is not determined as stable.
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. Persistent toxicities (grade 2 or greater) from any cause, except for liver function abnormalities due to underlying disease.
12. Pregnant or breast-feeding women.
13. 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.
14. Immunocompromised patients e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV).
15. Patients requiring percutaneous endoscopic gastrostomy (PEG) tubes.
16. Patients requiring treatment with inhibitors or inducers of CYP3A4 (see Section 7.11 for guidelines and wash-out periods).

Restrictions: Contraception

Female subjects must be post-menopausal, surgically sterile, or use two reliable forms of contraception from study enrolment and for 12 weeks after the last dose of either study drug. Reliable methods of contraception should be used consistently and correctly; acceptable methods include:

- 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 any one of the following:

- 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 study drug and for 12 weeks after the last dose.

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. However, because of the potential of radiosensitisation with Gemcitabine, caution should be exercised and radiotherapy should normally not be administered in the 3 days following Gemcitabine administration.

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 trial.

Test product, dose and mode of administration, batch no.: KU-0059436 (melt extrusion tablet and capsule).

Duration of treatment:

Dose escalation Phase: A run in phase will be used one week prior to commencing the first cycle of chemotherapy to allow samples to be taken for KU-0059436 alone pharmacokinetics. During the run-in phase, KU-0059436 will be administered twice daily for 3 consecutive days (–7 through –5) and then in the morning only on day –4 after a pre-treatment PK sample has been taken. No further doses of KU-0059436 will be taken by the patient prior to their first dose of chemotherapy, allowing a washout period prior to the chemotherapy. No run in, washout or pre-treatment PK samples will occur in a discontinuous KU-0059436 dosing cohort. Gemcitabine will be administered on days 1, 8, 15 and 22 of cycle 1 and on days 1, 8 and 15 for all other cycles. Each treatment cycle will consist of 28 days. KU-0059436 will be recommenced a minimum of 6 hours after the first treatment with Gemcitabine on day 1 as a single dose, all subsequent days KU-0059436 will be taken twice daily (unless in a discontinuous dosing cohort).

Treatment cycles will be repeated for up to 6 cycles or until progression of disease, intolerable toxicity, refusal of continued treatment by the patient, or investigator decision leads to their discontinuation from the study. Wherever possible, all patients should continue therapy for up to 6 cycles unless disease progression or rapid clinical deterioration is documented. Further drug administration, in excess of 6 cycles, shall be permitted if patients have at least stable disease or at the discretion of the clinical investigator.

Dose expansion phase: KU-0059436 will be administered twice daily continually throughout all cycles of treatment commencing on Day 1 (unless a discontinuous dosing schedule is chosen). Subsequent administrations will be as in the dose escalation phase.

Reference therapy, dose and mode of administration, batch no.: Gemcitabine

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 and Gemcitabine administered intravenously alone or in combination.

Efficacy: Although tumour response is not the primary endpoint of this study, patients with measurable disease will be assessed by RECIST criteria. For the expansion phase patients are required to have measurable disease assessed at baseline and have received 1 cycle of treatment and at least one follow up tumour assessment.

Pharmacokinetic data will also be collected, but not for the tablet escalation and expansion phases of the study.

Statistical methods:

Dose Escalation

Demographic data will be displayed, and summary statistics will be used, to describe the study population. Adverse events will be tabulated by body system, severity and relation to treatment. Efficacy data will be tabulated and a summary status produced.

Pharmacokinetic parameters will be calculated using non-compartmental analyses using WinNonLin.

The following parameters will be derived for KU-0059436 when dosed continuously alone and when dosed together with Gemcitabine: steady state C_{max} (maximum concentration achieved after drug administration), steady state t_{max} (time to C_{max}), steady state AUC_{0-12} (area under the curve across the dosing interval). For each individual patient, the C_{max} and AUC_{0-12} values obtained following dosing on day –4 (KU-0059436 alone data) will be compared with those obtained on day 8 of cycle 1 (KU-0059436 in combination data) to determine whether Gemcitabine has had any effect on plasma exposure to KU-0059436. For discontinuous dosing cycle 1 days 7 and 8 will be compared.

For Gemcitabine the following parameters will be derived when dosed alone (day 1 of cycle 1) or in combination with KU-0059436 (day 8 of cycle 1): C_{inf} (concentration at end of infusion, AUC_{0-4} and, if supported the data, terminal half life, AUC, clearance and volume of distribution. The individual patient values obtained following dosing on day 1 (Gemcitabine alone data) will be compared with those obtained on day 8 of cycle 1 (Gemcitabine in combination data) to determine whether KU-0059436 has had any effect on the plasma pharmacokinetics of Gemcitabine.

Dose Expansion

All patients in the expansion part of the study will be included in the analysis of the data. Demographic data will be displayed, and summary statistics will be used, to describe the study population. Adverse events will be tabulated by body system, severity and relation to treatment.

The objective response rate will be compared between the two treatment groups using Fisher's Exact Test. The objective response rate will be summarised and the 80% and 95% confidence intervals for the difference calculated using the Wilson score based method (Newcombe, RG).

Progression free survival and overall survival will be compared between the two treatment groups using a Cox proportional hazards model with a factor for treatment group. The effect of the combination group relative to Gemcitabine alone will be estimated by the hazard ratio together with its corresponding 80% and 95% confidence intervals. The hazard ratio will be calculated such that a value <1 will imply the treatment effect is in favour of the combination group. Summary statistics will also include the number of patients, number of events, median time to event and the 25th and 75th percentiles. Kaplan-Meier plots for progression free survival and overall survival will be presented by treatment group.

Analysis of the plasma concentration data will be carried out using non-linear mixed effects modelling via NONMEM in order to estimate individual patient KU-0059436 exposure, with a view to exploring exposure-response relationships.

TABLE OF CONTENTS
General Information
Synopsis of Protocol

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).

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).

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) and (Nguewa PA, Fuertes MA, Valladares et al).

1.2 Homologous Recombination Deficiency and PARP

Due to the molecular targeting of KU-0059436 to specific subsets of tumours, this has raised the opportunity for relatively less toxic cancer monotherapy using such a PARP-1 inhibitor compared with conventional treatments such as chemotherapy. The Investigational Medicinal Product (IMP) displays antitumour 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 (HR) 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 apoptosis (McCabe N, Farmer H, Lord C *et al.*) and (Farmer H *et al.*). 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 and 5-31% of ovarian cancers. This phenotype may also be present in cervical, head and neck and prostate cancers. The risk of pancreatic cancer is also increased in germ line BRCA mutation whilst late stage allelic inactivation of the BRCA 2 allele is commonly found in adenocarcinoma. Identification of the BRCAness phenotype has been reported to portend clinical benefit from drug therapy inducing DNA-damage (Turner N, Tutt A and Ashworth A). The Fanconi anaemia proteins are also involved in these DNA repair processes. Inactivation of the Fanconi anaemia/BRCA pathway in lung, oral cancer and cervical cancer cell lines by promoter hypermethylation may render these cells highly sensitive to DNA cross-linking agents (Marsit CJ, Liu M, Nelson HH *et al*) and (Narayan G, Arias-Pulido H, Nandula SV *et al*). Recent evidence indicating sensitivity of BRCA1 and BRCA2 deficient cells to PARP inhibition suggests that epigenetic modification of the Fanconi anaemia/BRCA pathway may lead to activity of PARP inhibitors in these tumour types.

2.0 RELEVANT PRE-CLINICAL RESULTS

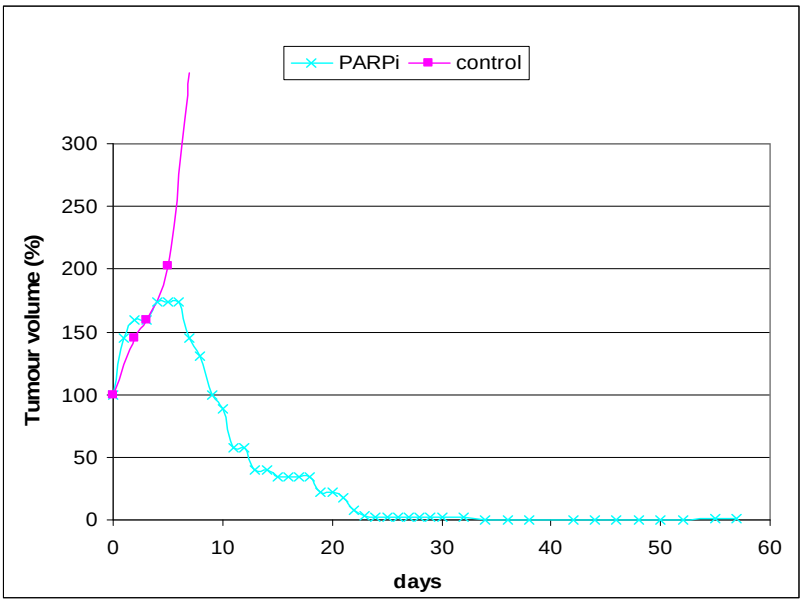
2.1 KU-0059436

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 dacarbazine and temozolomide.

2.2 Experimental Animal Models of BRCA Deficiency

In transgenic mouse knockout models, where either the BRCA1 or BRCA2 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 or BRCA2. The testing of the PARP inhibitor KU-0059436 in animals which develop spontaneous tumours shows, as discussed above, significant antitumour effects. The sustained use of inhibitor over 4 weeks or more leads to stasis and loss of tumour mass with no toxic effects observed in the animals. This activity is highly selective to these BRCA1 and BRCA2 deficient tumour masses only. Dosing studies in these models have indicated that the antitumour effects are slow to appear, i.e. a noted lag-phase is observed, but will occur following tumour cell division leading to significant effects (see Figure 1 below).

Figure 1 Efficacy of PARP inhibitor versus Control in the Kcre; BRCA1/2$^{flox/flox}$; p53$^{flox/flox}$ Model



- PARPi 50 mg/kg i.p. day 0-27
- Untreated control

The KU-0059436 molecule shows good cellular activity in the low nM range with a cellular dose for 50% inhibition (IC_{50}) of around 2 nM in HeLa cells.

2.3 Summary of Pre-clinical PK

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 [^{14}C]-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 IC_{50} 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 Overall Pre-clinical Summary

KU-0059436 is a potent inhibitor of PARP-1 which shows significant activity in

tumour cells deficient in BRCA1 and BRCA 2 genotypes and against tumour models or BRCA deficiency. 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. 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 (SAFETY AND EFFICACY)

3.1 The KU-0059436 Capsule

As of 21 November 2007, an estimated 205 patients have been recruited into 4 ongoing monotherapy studies and 4 ongoing studies of KU-0059436 in combination with one of the following chemotherapy agents: Dacarbazine, Gemcitabine, Carboplatin or Topotecan. Most of the exposure to date is in patients receiving KU-0059436 as a single agent, primarily from the first clinical study in man (KU36-92), a dose-escalation study in patients with advanced solid tumours. To date, 86 patients have been exposed to KU-0059436 in this study, and have received doses from 10 mg o.d. up to 600 mg b.d. (the dose at which dose limiting toxicity (DLT) was observed). Preliminary unvalidated data from 61 of the 86 patients have been carefully reviewed and indicate that KU-0059436 is generally well tolerated at doses up to 400mg b.d. in patients with solid tumours. The emerging safety profile is detailed in the current version of the Investigator's Brochure.

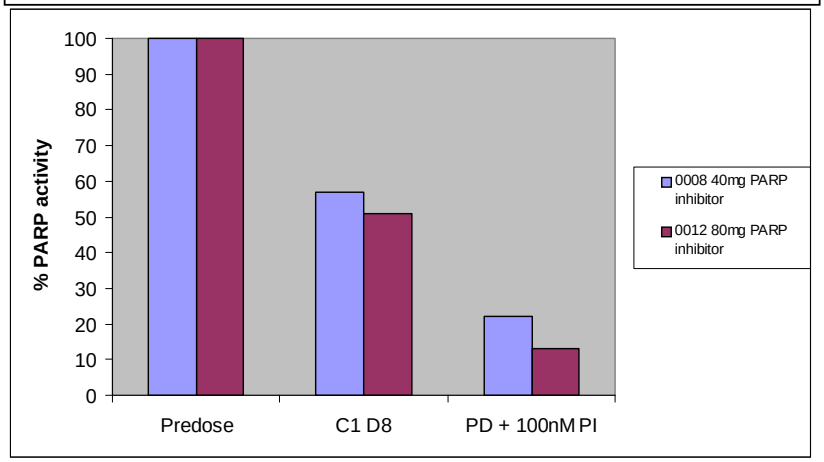
3.2 New Melt-Extrusion (Tablet) Formulation

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 within both the C_{max} and AUC_{ss} ranges in at least 95% of patients dosed to have BOTH their C_{max} within the range 1.37 to 11.8 ug/ml and their $AUC_{0\text{-}tau}$ within the range 6.66 to 106 ug.h/ml. 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.

3.3 Rationale for the Study

An ongoing phase I study in patients with advanced tumours (enriched with BRCA1 & BRCA2 patients) demonstrated that doses up to 400 mg b.d were tolerable with few toxicities being reported. A maximum dose of 400 mg KU-0059436, twice daily orally with continuous or discontinuous dosing has been selected for this protocol since effective inhibition of PARP-1 is essential.

Figure 2: PD: Tumour samples for PARP-1 inhibition



50% PARP Inhibition was seen in tumour biopsies in two patients, 8 and 12. (EudraCT No. 2005-001435-29).

Combination therapy of PARP-1 inhibitors with standard cytotoxic agents and rationale for a KU-0056434 and Gemcitabine combination study

Whilst the ability to repair DNA is desirable in most cases, in cancer therapy tumour cells are able to recover from chemotherapy insult prior to cell death thus preventing effective treatment. The potential to effectively prevent the DNA repair of a tumour cell following damage by a cytotoxic agent should therefore potentiate the effects of chemotherapy and may lead to better responses in some tumour types. This concept is supported by pre-clinical studies, and is now progressing to clinical trials of combinations of chemotherapeutic drugs and PARP-1 inhibitors such as KU-0059436.

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 2006-003826-26) has received regulatory clearance and is ongoing.

The scientific literature indicates that Gemcitabine induces stalled replication forks, signals through the ATM/ATR-CHK2/CHK1 pathway and is a potent radiosensitiser due to its impairment of homologous recombination function. It is known that PARP inhibition can selectively kill cells with homologous recombination defects, therefore the combination of Gemcitabine with KU-0059436 may be an effective anti-cancer combination. Supporting this hypothesis, a meeting abstract has indicated that PARP inhibitors will work effectively in combination with Gemcitabine in *in vitro* cell line as well as in pre-clinical models (Arnold M.A and Goggins M. *et al*.) and (Li *et al*). Studies have also indicated that a significant proportion of pancreatic cancers will have BRCA2 defects or may be deficient in other members of the homologous recombination repair pathway which suggests further potential utility of KU-0059436 in this tumour type.

Gemcitabine

Gemcitabine, alone or in combination with other chemotherapy, is often used in the treatment of patients who have advanced, metastatic or inoperable pancreatic cancer, non-small cell lung cancer, bladder cancer or breast cancer. However it only modestly improves survival by about one month compared to 5-FU alone, together with some relief of symptoms. There has been little improvement in the management of pancreatic carcinoma since Gemcitabine was introduced in 1996. From its mechanism of action it is anticipated that its activity may be increased when given in combination with KU-0059436. Consequently, the dose escalation phase of the study will start with a dose of 800mg/m^2 Gemcitabine, this dose has been shown to be active in chemo-naïve patients with pancreatic cancer (Carmichael et al, 1996) and breast cancer (Carmichael et al, 1995).

4.0 STUDY OBJECTIVES

4.1 Primary objective

To investigate the safety and tolerability and establish either the dose of KU-0059436 which is:

- the Maximum Tolerated Dose (MTD) of KU-0059436 administered orally in combination with Gemcitabine to patients with advanced malignant solid tumours.

Or if an MTD cannot be determined:

- a tolerable and effective dose of KU-0059436 in combination with an active dose of Gemcitabine (in the opinion of the investigators and sponsor).

4.2 Secondary objectives

- To identify the Dose Limiting Toxicity (DLT) of the combination of KU-0059436 and Gemcitabine.
- To determine the plasma pharmacokinetic profile of KU-0059436 alone and in combination with Gemcitabine.
- To determine the plasma pharmacokinetic profile of Gemcitabine alone and in combination with KU-0059436. To enable a preliminary assessment of the anti-tumour activity of KU-0059436 when given in combination with Gemcitabine compared to Gemcitabine alone in terms of progression free survival (PFS), overall survival (OS) and maximum tumour reduction.
- To determine the safety and tolerability profile of the KU-0059436 Melt-Extrusion [tablet] formulation in combination with Gemcitabine.
- To select a dose of KU-0059436 tablet and capsule in combination with Gemcitabine for further studies.

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 TRIAL POPULATION

Dose escalation phase: male or female patients with histologically or – where acceptable - cytologically confirmed advanced malignant solid tumours, refractory to standard therapy or for which no suitable effective standard therapy exists or for which Gemcitabine would be considered a potential treatment option. A maximum of 47 evaluable patients will be enrolled in the dose escalation part of the study

Dose expansion/escalation phase (tablet): male or female patients with histologically or cytologically diagnosed pancreatic cancer who are chemo-naïve. A maximum of 23 evaluable patients will be enrolled in the dose expansion part of the study.

6.0 INCLUSION AND EXCLUSION CRITERIA

6.1 Inclusion Criteria

1. Fully-informed written consent.
2. Dose escalation phase (capsule):
   Histologically or – where acceptable - cytologically confirmed malignant solid tumour refractory to standard therapy or for which no suitable effective standard therapy exists or for which Gemcitabine would be considered a potential treatment option.
   Dose escalation phase (tablet):
   a. Histologically or cytologically confirmed adenocarcinoma of the pancreas.
   b. Locally advanced or metastatic unresectable disease.
   Dose expansion phase (capsule):
   a. Histologically or cytologically confirmed adenocarcinoma of the pancreas.
   b. Locally advanced or metastatic unresectable disease.
3. Clinical or radiological evidence of disease. Measurable disease at baseline is only mandatory for the dose expansion part of the study (lesions that can be accurately measured in at least one dimension as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan).
4. Age ≥ 18 years.
5. Adequate bone marrow, hepatic (with stenting for any obstruction, if required) and renal function including the following:
   a. Haemoglobin ≥ 10.0 g/dl, absolute neutrophil count ≥ 1.5 x 10^9/L, platelets ≥100 x 10^9/L;
   b. Total bilirubin ≤ 1.25 x upper normal limit. For patients with advanced pancreatic cancer, total bilirubin ≤ 2.0 x upper normal limit
   c. AST (SGOT), ALT (SGPT) ≤ 2.5 x upper normal limit;

d. Creatinine ≤ 1.5 x upper normal limit.

6. Performance status (PS) ≤ 2 (ECOG scale).
7. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of trial.
8. 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.
9. Life expectancy of at least 12 weeks.

6.2 Exclusion Criteria

1. Dose escalation phase (capsule):
   Any anti-cancer chemotherapy, radiotherapy (except for palliative reasons), endocrine- or immunotherapy or use of other investigational agents administered within four weeks prior to start of study treatment. 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 the event below:
   - Significant treatment delays in previous chemotherapy courses due to bone marrow toxicity

   Dose escalation phase (tablet):
   No anti-cancer chemotherapy, radiotherapy (excluding palliative radiotherapy administered more than 4 weeks prior to study entry), endocrine- or immunotherapy or use of other investigational agents.
   Dose expansion phase (capsule):
   No anti-cancer chemotherapy, radiotherapy (excluding palliative radiotherapy administered more than 4 weeks prior to study entry), endocrine- or immunotherapy or use of other investigational agents.
2. Major surgery within 4 weeks of starting the study and patients must have recovered from effects of major surgery.
3. Patients with active second primary cancer, except adequately treated basal skin cancer or carcinoma in-situ of the cervix.
4. Clinically significant cardiovascular disease as defined by one or more of the following:
   - history of clinically significant congestive heart failure;
   - history of unstable angina pectoris or myocardial infarction up to 6 months prior to trial entry;
   - presence of severe valvular heart disease;
   - presence of a ventricular arrhythmia requiring treatment.
5. Known rapidly deteriorating liver function (≥2 x ULN rise in AST/ALT in the week preceding the study).
6. 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 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. Patients with known brain tumours or metastases will be excluded from this clinical trial if their disease is not determined as stable.

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. Persistent toxicities (grade 2 or greater) from any cause, except for liver function abnormalities due to underlying disease.
12. Pregnant or breast-feeding women.
13. 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.
14. Immunocompromised patients, e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV).
15. Patients requiring percutaneous endoscopic gastrostomy (PEG) tubes.
16. Patients requiring treatment with potent inhibitors or inducers of CYP3A4 (see Section 7.11 for guidelines and wash-out periods).

6.3 Restrictions/Precautions

6.3.1 Contraception

Female subjects must be post-menopausal, surgically sterile, or use two reliable forms of contraception from study enrolment and for 12 weeks after the last dose of either study drug. Reliable methods of contraception should be used consistently and correctly; acceptable methods include:

- 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 any one of the following:

- 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 study drugs 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. However, because of the potential of radiosensitisation with Gemcitabine, caution should be exercised and radiotherapy should normally not

be administered in the 3 days following Gemcitabine administration.

6.3.3 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 trial.

7.0 INVESTIGATIONAL PLAN

7.1 Trial Design

This is an open-label, multi-centre, phase I study of KU-0059436 when administered orally in combination with Gemcitabine to patients with advanced solid tumours (dose escalation phase) and advanced pancreatic cancer (dose expansion phase). The study consists of two distinct phases:

(i) a dose-escalation phase that may test both continuous and/or discontinuous KU-0059436 (capsules) dosing to establish the MTD, or a dose of KU-0059436 (capsules) in combination with an active dose of Gemcitabine that can be administered safely. The dose escalation phase for KU-0059436 capsules will be split into two parts: a continuous dosing schedule for KU-0059436 (capsules) and a discontinuous dosing schedule for KU-0059436 (capsules) that may be initiated dependant on emerging safety data to enable administration of an effective dose of KU-0059436.

In a separate dose escalation process, a maximum of 12 patients will be enrolled to determine a tolerable dose of KU-0059436 Melt-Extrusion [tablet] formulation in combination with Gemcitabine for future studies.

Combination doses with both the KU-0059436 capsule and tablet will be explored with Gemcitabine.

Continuous dosing or discontinuous dosing schedules may be administered. Possible discontinuous dosing schemes (capsules/tablets) that may be tested are:

- Discontinuous KU-0059436 bid 21 days on (D1-21) and 6 days off (D22-28)
- Discontinuous KU-0059436 bid 14 days on (D1-14) and 14 days off (D15-28)
- Discontinuous KU-0059436 bid 7 days on (D1-7) and 21 days off (D8-28)

(ii) a dose-expansion phase of the selected combination dose compared to Gemcitabine alone. The dose expansion phase of the study will further establish the safety and preliminary response data of the two treatment groups.

The dose expansion phase will be randomised (2:1) between a combination of KU-0059436 plus Gemcitabine versus Gemcitabine alone. The stratification for randomisation will be based on severity of disease, i.e., locally advanced or metastatic unresectable disease.

Each cycle of treatment will last for four weeks.

KU-0059436 will be administered twice daily continuously (unless in a discontinuous

dosing cohort) apart from the exceptions noted below.

Gemcitabine will be administered on days 1, 8, 15 and 22 of cycle 1 and on days 1, 8 and 15 for all other cycles.

Run-in phase:

A run-in phase will be used one week prior to commencing the first cycle of chemotherapy in the dose escalation with continuous dosing part of the study to allow samples to be taken for KU-0059436 pharmacokinetics. During the run-in phase, KU-0059436 will be administered twice daily for 3 consecutive days (–7 through –5) and then in the morning only on day –4 after a pre- treatment PK sample has been taken. No further doses of KU-0059436 will be taken by the patient prior to their first dose of chemotherapy, allowing a washout period prior to the chemotherapy. The PK sampling timelines are detailed in section 10.1 of the protocol and in the Bioanalytical Sample Handling plan.

No run-in phase will occur prior to commencing the first cycle of chemotherapy in the discontinuous dosing part of the study.

Dose escalation phase (continuous and discontinuous dosing)

In cycle 1, KU-0059436 will be administered orally twice-daily, Days 1 (p.m. only) through 28 at an escalating dose for each new cohort in combination with Gemcitabine administered on Days 1 (at least 6 hours before the first KU-0059436 administration), then days 8, 15 and 22, at least 1 hour after the patient has taken their KU-0059436 capsules.

For subsequent cycles, KU-0059436 will administered orally twice-daily, Days 1 through 28 (unless in a discontinuous dosing cohort) with Gemcitabine administered on Days 1, 8 and 15 given at least 1 hour after the patient has taken their KU-0059436 capsules. Cycles will be repeated every 28 days. 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 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 up to 6 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.

Each cohort will comprise a minimum of 3 patients during the dose-escalation phase. It is anticipated that a maximum of 47 patients may be enrolled in this part of the study. In the dose-expansion part of the study, up to 23 patients may be enrolled but the data will be reviewed on an ongoing basis and if the data are acceptable in terms of safety and response, patients will continue to be enrolled.

Dose expansion phase

There will be no run-in part in the expanded part of the study. Patients will be

administered KU-0059436 twice daily on days 1 through 28 for all cycles (unless a discontinuous dosing schedule is chosen). Gemcitabine will be administered on days 1, 8, 15, and 22 in cycle 1 and on days 1, 8 and 15 of subsequent cycles. Population pharmacokinetics for KU-0059436 only will be conducted in this part of the study.

Tumour evaluation (RECIST) will be conducted at the end of every 2 cycles and tumour markers (CEA and CA-199) will be assessed at the end of each cycle.

Once the appropriate dose of Gemcitabine + KU-0059436 combination therapy has been determined, patients enrolled in the expansion phase may undergo local genetic testing for their BRCA 1/2 mutation status if they sign a separate consent form. This data will be used for exploratory analysis of the anti-tumour response in this subpopulation.

7.2 Number of Patients

It is expected that a maximum of 47 evaluable patients will be enrolled in the dose escalation part of the study and a maximum of 23 evaluable patients will be enrolled in the expansion part.

The key objective for the expansion part is to establish the level of activity for the combination of Gemcitabine and KU-0059436, as represented by the objective response rate. Based on a number of publications, the response rate for Gemcitabine in metastatic pancreatic cancer is around 10%. The randomisation ratio for this study is 2:1 in favour of the combination arm, to gain more information on the combination.

Assurance calculations have been performed to determine the chance of success (ie superiority) in a Phase III study given a plausible range of results we might see in the expansion phase of the current study. The calculations show only a small increase in assurance if based on 45 patients compared to the 23 patients currently randomised in the expansion phase. Therefore it has been decided not to expand to 45 patients as was previously planned.

7.3 Registration of Patients

Prior to registration, the patients must give written informed consent for the trial and must complete all the pre-trial evaluations described in section 9.0. Patients must meet all the eligibility requirements listed in section 6.0.

7.4 Treatment Dose and Schedule

Patients will receive prophylactic anti-emetic therapy, e.g. metoclopramide, before Gemcitabine administration if deemed necessary by the investigator.

Continuous dosing cohorts with KU-0059436 capsule

In the Dose Escalation Phase of the study KU-0059436 will be increased from 50 mg twice daily to at least 200 mg twice daily over 3 cohorts of patients together with 800 mg/m^2 of Gemcitabine (Table 1) unless dose limiting toxicity of the drug-combination occurs. If these combinations are tolerable then the dose of Gemcitabine will be increased to 1000 mg/m^2 and KU-0059436 will be subsequently increased to a

maximum 400 mg twice daily. In the event that KU-0059436 in combination with Gemcitabine is not tolerated, intermediate doses up to 400 mg b.d. of KU-0059436 may be explored with lower doses of Gemcitabine (not below 600 mg/m^2).

At least three patients treated in a cohort must undergo repeated safety evaluations, up to and including Day 28, before enrolment of patients in the next dose cohort begins. Also, within any one cohort, the first patient must be observed for at least 7 days before further patients are recruited to that cohort. No intra-patient dose-escalation will be sanctioned. Decisions to escalate to the next level, or, when appropriate, to an intermediate dose level, will be made jointly by the investigator and the sponsor's Responsible Medical Officer based on review of all the available data. The protocol will additionally allow for treatment omissions and dose-adjustment of Gemcitabine, dependent on emerging toxicities.

If one patient in a cohort of at least three patients experience a dose-limiting toxicity 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.

The Gemcitabine dose level will not be reduced below 600 mg/m^2 unless it is deemed by the investigator that the patient is receiving clinical benefit from the combination of drug therapy.

Pharmacokinetic (PK) evaluations may 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 Gemcitabine.

Table 1 : Proposed Dose Escalation Schedule (continuous dosing with capsules)[$]

Cohort	Patient numbers	Phase	Gemcitabine dose*	KU-0059436 dose
1	3-6	Dose Escalation	800 mg/m^2	50 mg b.d.
2	3-6	Dose Escalation	800 mg/m^2	100 mg b.d.
3	3-6	Dose Escalation	800 mg/m^2	200 mg b.d.
4	3-6	Dose Escalation	1000 mg/m^2	200mg b.d.
5	3-6	Dose Escalation	1000 mg/m^2	400mg b.d.

*BSA should be measured in accordance with normal clinical practice.
[$]Other dose combinations may also be explored within this protocol depending upon emerging safety data.

Other dose combinations may also be explored within this protocol with conservative dose escalation of not more than 100% dependant on emerging safety data. The KU-0059436 dose will not go below 50mg o.d. or above 400mg b.d. and the dose of Gemcitabine will not be reduced below 600 mg/m^2 or increased above 1000 mg/m^2, any dose combination outside these ranges will require prior ethics and regulatory authority approval.

Discontinuous dosing cohorts with KU-0059436 capsule

Discontinuous dosing of KU-0059436 may be explored with dose equivalents of KU-0059436 that have been tested in previous escalations to enable delivery of effective doses of KU-0059436.

Dependant on the toxicities noted the discontinuous dosing schemes that may be tested are:

- Discontinuous KU-0059436 bid 21 days on (D1-21) and 6 days off (D22-28)
- Discontinuous KU-0059436 bid 14 days on (D1-14) and 13 days off (D15-28)
- Discontinuous KU-0059436 bid 7 days on (D1-7) and 21 days off (D8-28)

The discontinuous doses that are tolerated may also undergo a conservative dose escalation scheme, the escalations will not be more than 100% and the dose of KU-0059436 will not go above 400mg b.d. and the dose of Gemcitabine will not go above 1000 mg/m^2, any dose combination outside these ranges will require prior ethics and regulatory authority approval.

Discontinuous dosing cohorts with KU-0059436 tablet

Once a tolerable dose combination has been determined of discontinuous KU-0059436 capsule, a dose escalation scheme will be initiated to determine a tolerable schedule of discontinuous KU-0059436 tablet with Gemcitabine. The starting dose of KU-0059436 and Gemcitabine will be no more than the 100 mg bd KU-0059436 and 600mg/m^2 Gemcitabine determined to be tolerable in the discontinuous escalation cohorts with KU-0059436 capsule.

Table 2: **Proposed Dose Escalation Schedule (discontinuous dosing with tablets)**

Cohort	Patient numbers	Phase	Gemcitabine dose*	KU-0059436 dose
1	3-6	Dose Escalation	600 mg/m^2	100 mg o.d. D1-14
2	3-6	Dose Escalation	600 mg/m^2	100 mg b.d. D1-14

Other dose combinations or dosing schedules may also be explored within this protocol with conservative dose escalation of not more than 100% dependant on emerging safety data. The KU-0059436 dose will not go below 100mg o.d. or above 200mg b.d. and the dose of Gemcitabine will not be reduced below 600 mg/m^2 or increased above 1000 mg/m^2, any dose combination outside these ranges will require prior ethics and regulatory authority approval. Dependant on the toxicities noted the discontinuous dosing schemes that may be tested are:

- Discontinuous KU-0059436 bid 21 days on (D1-21) and 7 days off (D22-28)
- Discontinuous KU-0059436 bid 14 days on (D1-14) and 14 days off (D15-28)
- Discontinuous KU-0059436 bid 7 days on (D1-7) and 21 days off (D8-28)

If the above schedules are not tolerable, alternate schedules maybe tested, this may include offsetting the start dose of KU-0059436 after the Gemcitabine infusion, to avoid dosing KU-0059436 at the C_{max} of Gemcitabine, which may reduce toxicity and/or other discontinuous KU-0059436 schedules consisting of KU-0059436 administered for pre-defined numbers of days within each treatment cycle maybe explored.

7.5 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 (combination of both KU-0059436 and Gemcitabine) events experienced during Cycle 1:

- Grade 4 haematological toxicity, which lasts at least 5 days.
- Grade 3 or 4 febrile neutropenia.
- Grade 3 or greater non-haematological toxicities; this includes grade 3 or greater diarrhoea, nausea or vomiting despite adequate treatment.
- Patients who are unable to be dosed for more than 3 weeks (including rest period) due to 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 if considered clinically appropriate by the investigator.

Any patient in whom a toxicity equivalent to a DLT occurs during any cycle will have his or her treatment delayed until toxicity resolves to baseline or grade 1 or better.

7.6 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. It is also possible that a maximum dose that can be safely administered to patients will be determined (by the sponsor and investigators) prior to reaching the formal MTD. If no MTD is observed, a tolerable and effective dose of KU-0059436 (as determined in other studies) in combination with an active dose of Gemcitabine may be selected for future studies.

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.

7.7 Intra-patient Dose Modification - Gemcitabine and KU-0059436

In case of significant haematological or non-haematological toxicity only Gemcitabine doses may be modified. The major toxic effects of Gemcitabine are myelosuppression, fever, fatigue, diarrhoea, nausea and vomiting and predominantly mild skin rash. A significant number of patients (up to 17%) are also likely to develop Grade 3 or 4 transaminase elevations. It is therefore important that haematological data is available for review prior to Gemcitabine administration. Biochemical data should be available at least weekly for all cycles or otherwise when clinically indicated.

Where significant toxicity is present the dose of Gemcitabine may be omitted or reduced according to usual clinical practice. Where doses are omitted Gemcitabine should be administered at the next scheduled dosing time. When the Gemcitabine is omitted due to a toxicity that is related to Gemcitabine, the KU-0059436 dose may be continued at the Investigator's discretion.

7.7.1 Gemcitabine Dose Modifications for Haematological Toxicity within a cycle

The absolute neutrophil count (ANC) must be ≥1,500 x 10^6/l and the platelet count must be ≥100,000 x 10^6/l in order to administer full doses of Gemcitabine and KU-0059436 on day 1 of the cycle. Patients receiving Gemcitabine should be monitored prior to each dose for platelet, leukocyte, and granulocyte counts, and, if necessary, the dose of Gemcitabine may be either reduced or withheld in the presence of haematological toxicity that may be treatment related, according to the following scale (Table 3):

Table 3: Gemcitabine Dose Modifications for Haematological Toxicity

Absolute Granulocyte Count (x 10^6 /l)		**Platelet Count (x 10^6 /l)**	**% of Full Dose**
≥1,000	and	≥100,000	100
≥500-<1,000	or	≥50,000-<100,000	75
<500	or	<50,000	omit dose

7.7.2 Gemcitabine Dose Modifications for Non-Haematological Toxicities

Table 4: Gemcitabine Dose Modifications for Non-Haematological Toxicities

Event	Action
Grade 2, 3 or 4 toxicity (excluding nausea, vomiting and grade 2 diarrhoea and alopecia, if not judged as clinically significant by the investigator) present on the day of scheduled treatment.	For grade 2 toxicity, delay until resolution to grade 1 or baseline. For grade 3 or 4 toxicity, delay until resolution to grade 1 or baseline. Then reduce Gemcitabine dose level at which the patient experienced the toxicity (grade 3 reduce to 75%, grade 4 reduce to 50%) or omit a dose which-ever is felt to be most clinically appropriate.

Pulmonary toxicity: Transient dyspnoea occurs in <10% of patients after Gemcitabine, secondary to mild bronchospasm. Rarely, more severe pulmonary toxicity characterised by tachypnoea, hypoxia diffuse interstitial infiltrates, ARDS and respiratory failure may also occur. This is probably due to a capillary leak syndrome, which is noted with some nucleoside analogues. It is important to recognise early possible toxicity of this kind as it resolves with steroid treatment. The patient should be withdrawn from treatment.

7.7.3 Dose adjustments for Gemcitabine for subsequent cycles

ANC must be ≥1,500 x 10^6/L and platelet count must be ≥ 100,000 x 10^6/L before a new cycle of therapy may start. Patients who developed febrile neutropenia, platelets <25,000 x 10^6/L or bleeding associated with thrombocytopenia should be dosed at 75% of the starting dose of the previous cycle as should patients who developed grade 3 non-haematological toxicity (except nausea/vomiting) during the previous cycle. Patients who developed grade 4 non-haematological toxicity (except nausea/vomiting)

during the previous cycle should be dosed at 50% of the starting dose of the previous cycle or should be withdrawn from the study, whichever is most clinically appropriate. The dose reduction should apply to all injections during a cycle.

Patients who are dose reduced will continue to be dose at this reduced dose.

Patients unable to be dosed for in excess of 3 weeks (including the rest period) due to toxicity will be regarded as exhibiting dose limiting toxicity and the patient will be withdrawn from the study.

7.7.4 Dose adjustments for KU-0059436 for subsequent cycles

There will be no dose adjustments.

7.8 Duration of Study

Combination treatment with KU-0059436 and Gemcitabine may continue for as long as the Investigator feels that the patient is receiving benefit and is free from intolerable toxicity. In the event that Gemcitabine is permanently discontinued on the basis of Gemcitabine related toxicity or patients have completed the required treatment course, treatment with KU-0059436 may continue alone. At the discretion of the PI and in consultation with AstraZeneca, the patient may receive up to the optimal recommended monotherapy dose (i.e.: 400 mg bd capsule), however once a dose is selected patients may not escalate the KU-0059436 again.

Patients in the escalation phase, who have been on study treatment for over 6 cycles, will have a Final study assessment as per the Final Visit schedule - this will be the last data point recorded for each escalation phase patient for the purpose of the clinical study. The final analysis of the study data will occur once the last escalation phase patient recruited has completed the Final visit after 6 cycles of treatment or when approximately 20 deaths have occurred in the expansion cohort, whichever is the latter. Patients who remain on KU-0059436 after this time point will be monitored in line with the clinical protocol or as defined by local clinical practice. 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 anticipated duration of the trial (defined as FSI to last patient stopping treatment) is 48 months.

7.9 End of Study

The end of this study is defined as the date when all patients have stopped receiving KU-0059436. The final analysis of the study data will occur once the last escalation phase patient recruited has completed the Final visit after 6 cycles of treatment or when approximately 20 deaths have occurred in the expansion cohort, whichever is the latter. At this time point, the clinical study database will close to new data and the study data will be analysed and reported. Patients are however permitted to continue to receive KU-0059436 beyond the closure of the clinical study database if, in the opinion of the investigator, they are continuing to receive benefit from treatment with KU-0059436. For patients who do continue to receive treatment beyond the date of the closure of the clinical study database, Investigators will continue to report all new SAEs to the sponsor's representative Theradex until 30 days after study treatment is discontinued. Additionally any new SAE that is ongoing at the time of the closure of

the clinical study database, 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. Patients on monotherapy KU-0059436 at the "final visit" it is recommended should attend visits at least every 6 weeks (section 9.7), until they meet the discontinuation criteria (section 7.10).

7.10 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 Gemcitabine will continue for as long as the Investigator feels that the patient is receiving benefit and is free from intolerable toxicity. In the event that Gemcitabine is permanently discontinued on the basis of Gemcitabine related toxicity or patients have completed the required treatment course, treatment with KU-0059436 may continue alone. At the discretion of the PI and in consultation with AstraZeneca, the patient may receive up to the optimal recommended monotherapy dose (i.e.: 400 mg bd capsule). If Gemcitabine is permanently discontinued, patients will continue with study assessments as defined in section 9.7.

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

- Progressive disease that the investigator considers to be clinically significant,
- Disease progression that requires the initiation of any other anti-cancer treatment,
- Withdrawal of consent by the patient,
- Significant protocol violations including non-compliance with study procedures and patient lost to follow-up,
- Life-threatening or other unacceptable toxicity (in the investigator's opinion),
- Non-compliance with the treatment schedule,
- Changes in medical status of the patient such that the investigator believes that patient safety will be compromised,
- Serious intercurrent illness or significant worsening of intercurrent illness,
- 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 must 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 patient's underlying disease. Any new AEs that occur during the 30 day follow up following the final dose of study drug must be recorded (if SAEs then must be reported within 24 hours) and followed up as above.

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. 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 escalation patients remaining on study following 6 cycles of treatment, 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.

7.11 Concomitant Therapy

Patients are allowed to receive supportive care therapies (excluding cytokine growth factors) concomitantly during the trial. 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 trial), radiation therapy (except small field radiotherapy with palliative intent and at least 3 days must have elapsed since last dose of Gemcitabine) or experimental medications are permitted during the trial, or, if possible, for up to four weeks after the last KU-0059436 or Gemcitabine dose, whichever is administered last. Any disease progression that requires other specific anti-tumour therapy will be cause for discontinuation from the trial.

The following concomitant therapies warrant special attention:

Modifiers of CYP450 activity and other substances: 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.

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.

While 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:

- Fluvoxamine, fluconazole, fluoxetine, amiodarone, paroxetine, quinidine ketoconazole, itraconazole, ritonavir, idnavir, saquinavir, telithromycin, clarithromycin

For patients taking any of the above, the required wash-out periods prior to starting KU-0059436 are:

- Fluoxetine - 5 weeks; paroxetine - 2 weeks; any of the others - 1 week wash-out period

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

For patients taking any of the above, the required wash-out periods prior to starting KU-0059436 are:

- phenobarbitone 5 weeks, and for any of the others, 3 weeks.

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

Anticoagulant Therapy: Patients who are taking warfarin may participate in this trial; 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 is permitted where indicated.

Colony Stimulating Factors: The routine use of granulocyte colony stimulating factors (G-CSF) is not permitted during this trial. 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, i.e. complicated neutropenia. Patients who are on recombinant human erythropoeitin prior to trial entry may continue on this therapy. The use of recombinant erythropoeitin for patients not currently receiving erythropoeitin 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 trial or started during the trial or until 30 days from the end of the last protocol treatment which are different from the trial medication, must be documented.

8.0 PHARMACEUTICAL INFORMATION

8.1 KU-0059436 Delivery, Stability and Storage

The study drug KU-0059436 comes in 10 mg and 50 mg capsules. The capsules will be supplied in white high density polyethylene (HDPE) containers with child-resistant closures.

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

8.2 KU-0059436 Gelucire® 44/14 (Capsule) Preparation and Administration

KU-0059436 is supplied as Hydoxypropyl Methylcellulose (HPMC) white (50 mg) capsules and red (10 mg) capsules to be taken orally. Patients should swallow the medication whole with a glass of water during the morning and evening 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. KU-0059436 capsules should not be refrigerated. For shelf life and storage conditions, see drug label.

8.3 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 should not be refrigerated. For shelf life and storage conditions, see drug label.

8.4 KU-0059436 Accountability/Disposal

Patients will self-administer KU-0059436. A new bottle/s with the required number of capsules will be issued for the run-in period (dose escalation only) and on day 1 of each subsequent cycle. A member of the Investigative site's study team will query the patient for treatment compliance at each visit. All patients must return any used bottle/s of KU-0059436 prior to the beginning of the next cycle. An assessment of compliance (capsule count) of any remaining capsules 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 count and the information will be recorded in the appropriate section of the Case Report Form (CRF). After the capsule count has been performed, the remaining capsules 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 will be returned to AstraZeneca or its representative upon completion of the trial or destroyed at site following written approval from AstraZeneca.

8.5 Gemcitabine Delivery, Stability and Storage

It is expected that centres will use their commercial supply of Gemcitabine (Gemzar®) for this trial. 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**.** Gemcitabine 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 Case Report Forms.

8.6 Gemcitabine Preparation and Administration

Solution Preparation: Add normal saline to reconstitute the drug to a final concentration of 38 mg/ml (i.e. add 25 ml normal saline to 1 gm vial and 5 ml normal saline to 200 mg vial). The final calculated drug dose may be further diluted with up

to 100 ml normal saline. The reconstituted drug should be stored at controlled room temperature and must be used within 24 hours. Route of Administration: Intravenous only. Administer over 30 minutes.

Handling Precautions:

Gemcitabine is a toxic material which could cause skin and eye irritation. Ingestion or inhalation exposure of sufficient quantities could result in decreased white and red blood cells, hypo-spermatogenesis, gastrointestinal disturbances, and other signs of toxicity. The compound was positive in one of three tests for mutagenicity. Laboratory animal studies indicate that compounds in this therapeutic class may be a reproductive toxin and may induce foetal malformations. Avoid contact or inhalation.

8.7 Gemcitabine Accountability

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

9.0 SCHEDULE OF ASSESSMENTS, INVESTIGATIONS & SAMPLING

A cycle of treatment is scheduled to last 4 weeks (28 days). 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 trial 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-trial

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

Within 4 weeks prior to study dosing:

- Tumour evaluation (RECIST).
- Chest X-ray.

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 calculation of body surface area.
- Evaluation of performance status (ECOG).
- Concomitant medication and adverse events.
- Vital signs (heart rate, blood pressure, respiratory rate and temperature).
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Coagulation: INR and APTT (weekly in case patient is receiving warfarin).
- 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 and lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Biomarkers.
- Appropriate tumour maker (e.g. CEA and CA-199 for pancreatic cancer).
- Urinalysis: Dipstick for albumin, glucose, bilirubin and blood (microscopy if any more than one positive test).
- ECG.
- Urine **or** serum pregnancy test for females of reproductive potential (within 1 day or less prior to starting treatment).
- Tissue sample (optional): 9ml Blood sample to be stored at –80^{o}C for future potential pharmacogenetic assessment, subject to patients' separate consent.

9.3 On Trial Sampling and Assessment

The details of the investigations are explained in the text below, in Table 5 (dose escalation phase continuous dosing) and Table 6 (dose escalation phase discontinuous dosing) and Table 7 (dose expansion phase), and in the following sections.

9.3.1 Dose escalation phase continuous dosing

Run-in period

Day -7 (prior to treatment) – Examinations marked with (*) need not be repeated if already performed within 3 days:

- Urine or serum pregnancy test for females of reproductive potential prior to dosing.
- ***** Review of medical history including baseline symptoms and current medication.

- Review of AEs and current medication.
- ***** Brief physical examination and description of external signs of neoplastic disease.
- ***** Performance status (ECOG).
- Vital signs (including heart rate, blood pressure, respiratory rate and temperature).
- ***** Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- ***** Coagulation: INR and APTT (weekly in case patient is receiving warfarin).
- ***** 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- ***** Urinalysis: Dipstick for albumin, glucose, bilirubin and blood (microscopy if any more than one positive test).
- ***** ECG.
- Commence twice daily oral administration of KU-0059436
- PK sampling KU-0059436 (Day –4).
- The Patient Medication Record must be completed on each day of KU-0059436 intake.

Cycle 1

Day 1 (prior to treatment):

- Review of AEs and current medication.
- Brief physical examination and description of external signs of neoplastic disease.
- Performance status (ECOG).
- Vital signs (including heart rate, blood pressure, respiratory rate and temperature).
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- PK blood samples.
- 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Coagulation: INR and APTT (weekly in case patient is receiving warfarin)
- Appropriate tumour maker (e.g. CEA and CA-199 for pancreatic cancer).
- Urinalysis: Dipstick for albumin, glucose, bilirubin and blood (microscopy if any more than one positive test).
- Dispense KU-0059436.
- Commence twice daily oral administration of KU-0059436 **in the afternoon only, at least 6 hours post Gemcitabine administration)** and Gemcitabine intravenously.
- The Patient Medication Record must be completed on each day of KU-0059436 intake.

Day 8

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- PK sampling KU-0059436 and Gemcitabine.
- Administer Gemcitabine; KU-0059436 twice daily dosing continues.

Day 15

- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Administer Gemcitabine; KU-0059436 twice daily dosing continues.

Day 22

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Administer Gemcitabine; KU-0059436 twice daily dosing continues.

<u>Cycle 2 and subsequent cycles</u>

Day 1 (prior to treatment)

- Review of AEs and current medication.

- Physical examination.
- ECOG performance status.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Appropriate tumour maker (e.g. CEA and CA-199 for pancreatic cancer).
- INR and APTT (weekly in case patient is receiving warfarin).
- Urinalysis.
- ECG
- Administer Gemcitabine; dispense KU-0059436 and continue twice daily dosing.

Day 8

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Administer Gemcitabine; KU-0059436 twice daily dosing continues.

Day 15

- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Biomarkers (end of the cycle but can be taken from day 15 onwards)
- Administer Gemcitabine; KU-0059436 twice daily dosing continues.

Day 22

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Radiological assessment to be performed at the end of cycle two then every two cycles.

9.3.2 Dose escalation phase discontinuous dosing (tablet and capsule)

Possible discontinuous dosing schemes that may be tested are:

- Discontinuous KU-0059436 bid 21 days on (D1-21) and 6 days off (D22-28)
- Discontinuous KU-0059436 bid 14 days on (D1-14) and 13 days off (D15-28)
- Discontinuous KU-0059436 bid 7 days on (D1-7) and 21 days off (D8-28)

Cycle 1

Day 1 (prior to treatment):

- Urine or serum pregnancy test for females of reproductive potential prior to dosing.
- Review of AEs and current medication.
- Brief physical examination and description of external signs of neoplastic disease.
- Performance status (ECOG).
- Vital signs (including heart rate, blood pressure, respiratory rate and temperature).
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- PK blood samples (capsule only).*
- 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Coagulation: INR and APTT (weekly in case patient is receiving warfarin).
- Appropriate tumour maker (e.g. CEA and CA-199 for pancreatic cancer).
- Urinalysis: Dipstick for albumin, glucose, bilirubin and blood (microscopy if any more than one positive test).
- Dispense KU-0059436.
- Commence twice daily oral administration of KU-0059436 **in the afternoon only, at least 6 hours post Gemcitabine administration)** and Gemcitabine intravenously.
- The Patient Medication Record must be completed on each day of KU-0059436 intake.

Day 7

- PK blood samples (capsule only) *.

Day 8

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- PK sampling KU-0059436 and Gemcitabine (capsule only)*.
- Administer Gemcitabine.
- Administer KU-0059436 twice daily depending on the dosing schedule.

Day 15

- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Administer Gemcitabine.
- Administer KU-0059436 twice daily depending on the dosing schedule.

Day 22

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.

- Administer Gemcitabine.
- Administer KU-0059436 twice daily depending on the dosing schedule

Cycle 2 and subsequent cycles

Day 1 (prior to treatment)

- Review of AEs and current medication.
- Physical examination.
- ECOG performance status.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Appropriate tumour maker (e.g. CEA and CA-199 for pancreatic cancer).
- INR and APTT (weekly in case patient is receiving warfarin).
- Urinalysis.
- ECG
- Administer Gemcitabine; dispense KU-0059436 and continue twice daily dosing.

Day 8

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Administer Gemcitabine.
- Administer KU-0059436 twice daily depending on the dosing schedule.

Day 15

- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Biomarkers (end of the cycle but can be taken from day 15 onwards)
- Administer Gemcitabine.
- Administer KU-0059436 twice daily depending on the dosing schedule.

Day 22

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Administer KU-0059436 twice daily depending on the dosing schedule
- Radiological assessment to be performed at the end of cycle two then every two cycles.

*For patients receiving the discontinuous dosing schedule for KU-0059436 with Gemcitabine PK samples will only be taken if the dose combination has not been previously tested in the continuous dose escalation part of the study.
PK samples will only be taken on the D1-7, D1-14 and D1-21 capsule dosing schedules.

9.3.3 Dose Expansion Phase

Cycle 1

Day 1 (prior to treatment) – Examinations marked with (*) need not be repeated if already performed within 3 days of study entry:

- * Review of medical history including baseline symptoms and current medication.
- Review of AEs and current medication.
- * Brief physical examination and description of external signs of neoplastic disease.
- * Performance status (ECOG).
- Vital signs (including heart rate, blood pressure, respiratory rate and temperature).
- * Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, leukocyte count, differentials, absolute neutrophil count, lymphocytes and platelets.
- Appropriate tumour maker (e.g. CEA and CA-199 for pancreatic cancer).

- * Coagulation: INR and APTT (weekly in case patient is receiving warfarin).
- PK blood samples.
- * 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- * Urinalysis: Dipstick for albumin, glucose, bilirubin and blood (microscopy if any more than one positive test).
- * ECG.
- Dispense KU-0059436.
- Commence twice daily oral administration of KU-0059436 and Gemcitabine intravenously.
- The Patient Medication Record must be completed on each day of KU-0059436 intake.
- If patient consents a blood sample will be taken for BRCA 1 and BRCA 2 local genetic testing (if BRCA status has not been previously tested).

Day 8

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- PK sampling.
- Administer Gemcitabine and continue twice daily dosing of KU-0059436*.

Day 15

- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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 lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Administer Gemcitabine and continue twice daily dosing of KU-0059436*.

Day 22

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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,, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Administer Gemcitabine and continue twice daily dosing of KU-0059436*.

Cycle 2 and subsequent cycles

Day 1 (prior to treatment)

- Review of AEs and current medication.
- Physical examination.
- ECOG performance status.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Appropriate tumour maker (e.g. CEA and CA-199 for pancreatic cancer).
- INR and APTT (weekly in case patient is receiving warfarin).
- Urinalysis.
- ECG
- Administer Gemcitabine; dispense KU-0059436.

Day 8

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.

- Administer Gemcitabine and KU-0059436*.

Day 15

- Vital signs.
- Review of AEs and current medication.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Biomarkers (end of the cycle but can be taken from day 15 onwards)
- Administer Gemcitabine; and continue twice daily dosing of KU-0059436*.

Day 22

- Review of AEs and current medication.
- Vital signs (including heart rate, blood pressure, respiratory rate, temperature) and weight.
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Continue twice daily dosing of KU-0059436*.
- Radiological assessment prior to be performed at the end of every two cycles.

* With discontinuous dosing the KU-0059436 dosing may not continue dependant on the schedule.

9.4 Final Visit/Withdrawal of KU-0059436

The final visit is to occur after 6 cycles of treatment for patients in the escalation cohorts.

- 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).
- Performance status (ECOG).
- Haematology: haemoglobin, haematocrit, MCV, MHC, MHCV, erythrocytes, reticulocytes, 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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
- Urinalysis: Dipstick for albumin, glucose, bilirubin and blood (microscopy if more than one positive test).
- Tumour evaluation.
- Chest X-ray
- ECG

9.5 Patients continuing on combination therapy

This section applies to escalation patients continuing on KU-0059436 and chemotherapy after 6 cycles of treatment.

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 may continue to receive KU-0059436 and Gemcitabine 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 and up to 30 days after the last dose of KU-0059436 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 and new KU-0059436 supplies will be dispensed to the patient.

9.6 Follow-Up

A final Follow-up Visit should be conducted 30 days after the last dose of the study treatment(s). Haematology and biomarkers will be assessed. In addition, patients participating in the dose escalation phase will have a physical examination.

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 11.4.7) and appropriate safety evaluations repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow up, then this should be noted in the CRF.

9.7 Visit Schedule for patients continuing on monotherapy KU-0059436

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 Gemcitabine 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 the sponsor, the patient may receive up to the optimal monotherapy dose (i.e.: 400 mg bd capsule). Once a dose is agreed for the patient no dose further dose escalations will be allowed. When Gemcitabine is permanently discontinued and patients initiate KU-0059436 monotherapy:

- It is recommended patients be 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 22" (Table 6).
- Thereafter, it is recommended that safety assessments are performed every 6 weeks, as per the "Cycle 2 onwards Day 29/1" visit schedule (Table 6).
- During all the above visits nor 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 9.6).

Table 5: Schedule of Study Evaluations for Dose Escalation Phase (Continuous Dosing)

	Screening/base line	Run in period: **escalation phase only**				Wash out period: **escalation phase only**			Cycle 1 Day				Cycle 2 onwards Day[16]				Withdrawal of KU-0059436	Follow–up 30 days post last dose
		-7	-6	-5	-4	-3	-2	-1	1	8	15	22	29/1	8	15	22		
Eligibility criteria	x																	
Medical history [1]	x[1]	x*																
Physical exam[2]	x[2]	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	x	x	x	x	x	x
Con. Meds	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Vital Signs[3]	x	x							x	x	x	x	x	x	x	x	x	
Haematology[4]	x	x*							x	x	x	x	x	x	x	x	x	x
Coagulation[5]	x	x*							x				x					
Chemistry[6]	x	x*							x	x	x	x	x	x	x	x	x	
Tumour Markers	x								x				x					
Urinalysis[7]	x	x*							x				x				x	
Tumour Evaluation[8]	x															x	x	x
Pregnancy Test[9]	x																	
ECG	x	x*											x				x	
PK[10]		x			x				x	x	x							
Pharmacogenetics[11]	x																	
Biomarker[12]	x														x			x
Chest X-ray[13]	x																x	
KU-0059436[14]		x							x				x					
Gemcitabine [15]									x	x	x	x	x	x	x			
Pt Medication Record[14]		x	x	x	x				x	x	x	x						

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

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 trial a description of external signs of the neoplastic disease.
3. Includes heart rate, blood pressure, respiratory rate and temperature.
4. Hb, Hct, MCV, MHC, MHCV, erythrocytes, reticulocytes, leukocyte count, differentials, abs. neutrophil and lymphocyte count, platelets.
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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
7. Dipstick for albumin, glucose, bilirubin and blood (microscopy if more than one positive test).
8. Includes systematic use of clinical, radiographic and other methods for tumour evaluation. Baseline measurement to be performed within 4 weeks prior to treatment and the every 8 weeks until confirmed progressive disease.
9. Female patients with reproductive potential. Urine or serum sample.

PK samples:

10. Baseline samples will be taken on Days 1 and 8 prior to drug administration and for other times see protocol section 10.1. PK samples are not required after cycle 1.
11. Pharmacogenetic sample (9.0ml) to be collected preferably 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 (can be taken from day 15 onwards) and at follow up visit.
13. Chest X-ray within 4 weeks prior to first dose at baseline and at withdrawal.
14. **Capsules will be dispensed to allow:**

(a) twice daily dosing on days -7 though -5 and then once in the morning only on day -4
(b) Continuous twice daily dosing on days 1 through 28 inclusive (except for day 1 on which KU-0059436 is administered once only, 6 hours after Gemcitabine
(c) the Patient Medication Record must be completed with the exact times on each day of KU-0059436 administration during the run-in period, in cycle 1 and on PK sampling days during the escalation phase.

15. Gemcitabine will be administered weekly for each week of the first cycle and for three out of 4 weeks from cycle 2 onwards.
16. Patients receiving benefit from treatment with KU-0059436 and Gemcitabine can continue provided they are free from intolerable toxicity. In the event that Gemcitabine is permanently discontinued, treatment with KU-0059436 alone may continue (refer to table 6).

Table 6: Schedule of Study Evaluations for Dose Escalation Phase (Tablet and capsule Discontinuous Dosing)

	Screening/baseline	Cycle 1 Day					Cycle 2 onwards Day[18]				Final Visit/ Withdrawal of KU-0059436	Post 6 cycle visits per local practice during treatment[16]	Follow–up 30 days post last dose
		1	7	8	15	22	29/ 1	8	15	22			
Eligibility criteria	x												
Medical history[1]	x[1]												
Physical exam[2]	x[2]	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	x		
Tumour Markers	x	x					x						
Urinalysis[7]	x	x					x				x		
Tumour Evaluation[8]	x									x	x		x
Pregnancy Test[9]	x												
ECG	x	x					x				x		
PK[10]		x	x	x									
Pharmacogenetics[11]	x												
Biomarker[12]	x								x				x
Chest X-ray[13]	x										x		
KU-0059436[14]		x					x					x	
Gemcitabine [15]		x		x	x	x	x	x	x			x	
Pt Medication Record[14]		x	x	x	x								
SAE reporting only[17]												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 trial a description of external signs of the neoplastic disease.
3. Includes heart rate, blood pressure, respiratory rate and temperature.
4. Hb, Hct, MCV, MHC, MHCV, erythrocytes, reticulocytes, leukocyte count, differentials, abs. neutrophil and lymphocyte count, platelets.
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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
7. Dipstick for albumin, glucose, bilirubin and blood (microscopy if more than one positive test).
8. Includes systematic use of clinical, radiographic and other methods for tumour evaluation. Baseline measurement to be performed within 4 weeks prior to treatment and the every 8 weeks until confirmed progressive disease.
9. Female patients with reproductive potential. Urine or serum sample.

PK samples

10. In the discontinuous dosing schedule for KU-0059436 with Gemcitabine, PK samples will only be taken if the dose combination has not been previously tested in this study. If PK sampling is to occur baseline samples will be taken on Days 1, 7 and 8 prior to drug administration and for other times see protocol section 10. PK samples will only be taken on the D1-7, D1-14 and D1-21 capsule dosing schedules. PK samples are not required after cycle 1.
11. Pharmacogenetic sample (9.0ml) to be collected preferably 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 (can be taken from day 15 onwards) and at follow up visit.
13. Chest X-ray within 4 weeks prior to first dose at baseline and at withdrawal.
14. **Capsules will be dispensed to allow:**

(a) discontinuous dosing of KU-0059436 depending on the dosing schedule (capsules will be dispensed appropriately).
(b) the Patient Medication Record must be completed with the exact times on each day of KU-0059436 administration in cycle 1 and on PK sampling days during the escalation phase.

15. Gemcitabine will be administered weekly for each week of the first cycle and for three out of 4 weeks from cycle 2 onwards.
16. After 6 cycles of treatment, escalation patients may continue on KU-0059436 and Gemcitabine 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.
17. For escalation patients remaining on study following 6 cycles of treatment, 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.
18. Patients receiving benefit from treatment with KU-0059436 and Gemcitabine can continue on treatment provided they are receiving benefit and are free from intolerable toxicity. In the event that Gemcitabine is permanently discontinued, treatment with KU-0059436 alone may continue. If Gemcitabine is permanently discontinued, it is recommended patients be assessed according to the Cycle 2 onwards Day 1, Day 8, Day 15 Day 22 visit schedule for the first cycle of monotherapy KU-0059436 and thereafter every 6 weeks in line with the "Cycle 2 onwards - Day 29/1" visit schedule. All SAEs will be reported to Theradex within 24 hours of becoming aware of the event.

Table 7: Schedule of Study Evaluations for Dose Expansion Phase

	Screening/ Baseline	Cycle 1 Day				Cycle 2 onwards				Withdrawal of KU-0059436[17]	Follow up (30 days post last dose)[18]
		1	8	15	22	29/ 1	8	15	22		
Eligibility criteria	x										
Medical history [1]	x[1]	x*									
Physical exam[2]	x[2]	x*				x				x	
ECOG Performance	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	x	x	
Tumour Markers	x	x				x					
BRCA1/2 testing[16]		x									
Urinalysis[7]	x	x*				x				x	
Tumour Evaluation[8]	x								x		x
Pregnancy Test[9]	x										
ECG	x	x*				x				x	
PK[10]		x	x								
Pharmacogenetics[11]	x										
Biomarker[12]	x							x			x
Chest X-ray[13]	x									x	
KU-0059436[14]		x				x					
Gemcitabine [15]		x	x	x	x	x	x	x			
Pt Medication Record[14]		x	x	x	x						
Follow up for survival[18]											x

** Need not be repeated at day 1 if performed within 3 days of study entry*

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 trial a description of external signs of the neoplastic disease.
3. Includes heart rate, blood pressure, respiratory rate and temperature.
4. Hb, Hct, MCV, MHC, MHCV, erythrocytes, reticulocytes, leukocyte count, differentials, abs. Neutrophil and lymphocyte count, platelets.
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, lactic dehydrogenase [LDH]), serum amylase, serum lipase, bilirubin and uric acid.
7. Dipstick for albumin, glucose, bilirubin and blood (microscopy if more than one positive test).
8. Includes systematic use of clinical, radiographic and other methods for tumour evaluation. Baseline measurement to be performed within 4 weeks prior to treatment and the every 8 weeks until confirmed progressive disease.
9. Female patients with reproductive potential. Urine or serum sample.

10. PK samples will only be performed at designated sites: Baseline samples will be taken on Day 1 and Day 8 prior to drug administration and for other analysis consult lab sampling plan. PK samples are not required after cycle 1.
11. Pharmacogenetic sample (9.0ml) to be collected preferably 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 (can be taken from day 15 onwards) and at follow up visit.
13. Chest X-ray within 4 weeks prior to first dose at baseline and at withdrawal.
14. **Capsules will be dispensed on day 1 of each cycle:**
    (a) For continuous dosing to allow twice daily, days 1 through 28 inclusive. Discontinuous KU-0059436 dosing may administered dependant on emerging data (capsules will be dispensed appropriately).
    (b) the Patient Medication Record must be completed with the exact times on each day of KU-0059436 administration during the run-in period, in cycle 1 and on PK sampling days during the expansion phase.
15. Gemcitabine will be administered weekly for each week of the first cycle and for three out of 4 weeks from cycle 2 onwards.
16. Performed in the randomised phase only. Only patients who have not had BRCA1/2 status tested prior to involvement in the study and have given consent need to have a blood sample taken. Genetic counselling will be provided as per hospital procedures. Results are not required for randomisation.
17. Patients receiving benefit from treatment with KU-0059436 and Gemcitabine can continue provided they are receiving benefit and are free from intolerable toxicity. In the event that Gemcitabine is permanently discontinued, treatment with KU-0059436 alone may continue (refer to table 6).
18. All expansion patients will be followed for survival beyond the final treatment visits.

10.0 EFFICACY AND SAFETY EVALUATIONS

10.1 Pharmacokinetics

Appropriate scheduled sampling of blood for the analysis of the concentration of KU-0059436 and Gemcitabine will allow the assessment of drug pharmacokinetics in this combination schedule during the dose escalation part of the study in both continuous and discontinuous KU-0059436 dosing capsule cohorts (tablet cohorts will not be tested). See Table 8, Table 9 and Table 10. Detailed pharmacokinetic analysis will be obtained in the study to determine distinct pharmacokinetic profiles for (for the capsule formulation only):

* KU-0059436 when dosed alone
* KU-0059436 + Gemcitabine when dosed in combination
* Gemcitabine when dosed alone

Limited PK sampling for KU-0059436 will also be conducted during cycle 1 of the expansion phase of the study. See Table 11.

In the continuous dosing cohorts of the escalation phase only to accommodate the requirements of PK sampling, the escalation part of the study will have a run-in part in which KU-0059436 will be administered alone from Day –7 until the morning of Day –4 followed by a drug-free period of at least 2 days prior to cycle 1.

In both discontinuous and continuous dosing cohorts in the escalation phase, for Cycle 1, KU-0059436 will be administered once only on Day 1 (in the afternoon) and twice daily for the remainder of the cycle days 2 to 28 inclusive (unless a discontinuous dosing schedule is followed). Gemcitabine will be administered by a 30 min infusion on days 1, 8, 15 and 22. On day 1, Gemcitabine will be given at least 6 hours prior to KU-0059436 and on days 8 and 15, 1 hour after the first KU-0059436 dose (if applicable).

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

KU-0059436 Pharmacokinetics: Sampling schedule in the continuous dosing cohort

Samples to be taken on day –4 during the run-in period but not before 3 days of KU-0059436 administration:

Table 8: Pharmacokinetic Blood Collection Time Points (dose escalation phase continuous dosing only [capsule only])

Elapsed time	KU-0059436
0	Predose
30min	30mins
1 hr	1 hr
2hrs	2hr
3hrs	3hrs
4hrs	4hrs
5hrs	5hrs
7hrs	7hrs

Table 9: KU-0059436/Gemcitabine Pharmacokinetics: Inter-study sampling schedule dose escalation phase continuous dosing (capsule only)

Cycle	Day	Elapsed time	KU-0059436	Gemcitabine
Cycle 1:	Day 1	0		Prior to administration
		30min		30mins:[At the end of infusion (EOI)]
		45min		45 minutes
		1hr		1 hour
		1.5hr		1.5hrs
		2hrs		2hrs
		4hrs		4hrs
	Day 8	0	Predose	
		30min	30min	
		1hr	1hr	Prior to administration
		1hr 30min		30mins:[At the end of infusion (EOI)]
		1hr 45min		45 minutes
		2hrs	2hrs	1 hour
		2hrs 30mins		1.5hrs
		3hrs	3hrs	2hrs
		4hrs	4hrs	
		5 hrs	5hrs	4hrs
		7hrs	7hrs	

KU-0059436 Pharmacokinetics: Sampling schedule in the discontinuous dosing cohort (capsule only)

No run-in PK sampling will occur in discontinuous KU-0059436 dosing cohorts.

In the discontinuous dosing schedule for KU-0059436 with Gemcitabine, PK samples will only be taken if the dose combination has not been previously tested in this study.

Table 10: KU-0059436/Gemcitabine Pharmacokinetics: Inter-study sampling schedule dose escalation phase discontinuous dosing (capsule only)

Cycle	Day	Elapsed time	KU-0059436	Gemcitabine
Cycle 1:	Day 1	0		Prior to administration
		30min		30mins:[At the end of infusion (EOI)]
		45min		45 minutes
		1hr		1 hour
		1.5hr		1.5hrs
		2hrs		2hrs
		4hrs		4hrs
	Day 7	0	Predose	
		30min	30mins	
		1 hr	1 hr	
		2hrs	2hr	
		3hrs	3hrs	
		4hrs	4hrs	
		5hrs	5hrs	
		7hrs	7hrs	
	Day 8	0	Predose	
		30min	30min	
		1hr	1hr	Prior to administration
		1hr 30min		30mins:[At the end of infusion (EOI)]
		1hr 45min		45 minutes
		2hrs	2hrs	1 hour
		2hrs 30mins		1.5hrs
		3hrs	3hrs	2hrs
		4hrs	4hrs	
		5 hrs	5hrs	4hrs
		7hrs	7hrs	

Table 11: KU-0059436/Gemcitabine Pharmacokinetics: Inter-study sampling schedule (dose expansion phase).

Cycle	Day	Elapsed time	KU-0059436
Expanded part of the study: Cycle 1	1	0	Prior to administration
	8	+ 0 to 1.5 hrs	+ 0 to 1.5 hrs
		+ 1.5 to 3 hrs	+ 1.5 to 3 hrs
		+ 3 to 6 hrs	+ 3 to 6 hrs
		+ 6 to 12 hrs	+ 6 to 12 hrs

10.2 Biomarkers and Pharmacogenetics

Patients will provide samples for exploratory biomarker research at each of the visits referenced in the study flow chart subject to consent. The CRF will capture date and time of sample acquisition and time of freezing where relevant.

Patients will not be excluded from the trial if these samples are not collected/made available.

All analyses will be performed by an approved laboratory.

10.2.1 Blood samples for biomarker analysis

Blood samples will be collected pre dosing, end of cycle 2 (from day 15 onwards) and at follow up visit and stored for possible retrospective exploratory biomarker research.

10.2.2 Urine samples for biomarker analysis

Urine samples will be collected pre dosing, end of cycle 2 (from day 15 onwards) and at follow up visit and stored for possible retrospective exploratory biomarker research.

10.2.3 BRCA1 and BRCA2 testing

This is performed in the randomised phase only. Only patients who have not had BRCA1/2 status tested prior to involvement in the study and have provided written consent need to have a blood sample taken for BRCA 1/2 testing. Testing and genetic counselling will be provided as per hospital procedures. Results are not required for randomisation.

10.2.4 Pharmacogenetics samples

Patients will be requested to provide a blood sample 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.

10.3 Assessment of Anti-neoplastic Activity

CT or MRI Scans (RECIST)

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

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 follow-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 randomisation 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 requires 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.

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.

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).

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

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.

All medical images will be collected and archived centrally.

10.4 Clinical endpoints

Objective response rate:

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. Response is either a CR or PR. An overall best outcome will be derived based on the outcomes seen in the study.

Progression free survival:

Disease progression is based on RECIST criteria. Death in absence of disease progression will be counted as disease progression. Progression Free Survival is defined as time from randomisation to time to documented progression. Patients who have not progressed at the time of analysis will be censored using the last available assessment date.

Overall survival:

All patients in the expansion phase will be followed up for survival. Overall survival is defined as time from randomisation to time of death. Patients who have not died at the time of analysis will be censored using the last available date the patient was known to be alive. For those patients still alive, every effort will be made to assess their survival status as close to the planned Data Cut-Off point as possible.

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 a study drug, whether or not related to the study drug.

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 study drugs.

11.3.2 Lack of Efficacy

When there is deterioration in the condition for which the study treatment is being used, (i.e. advanced solid tumours or pancreatic 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 drug (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 10.4 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 drug 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 study drug and any concomitant treatment dispensed (or other action taken).

For patients permitted to continue to receive KU-0059436 (and Gemcitabine if applicable) 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. Patients continuing on KU-0059436 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. Patients continuing on KU-0059436 and Gemcitabine 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 section 9.7.

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 Time period for collection of AE / SAE

Expansion patients: non-serious adverse events and 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.

Escalation patients: non-serious adverse events and SAEs will be collected from the time consent is given, up to completion of the Final Visit after 6 cycles of treatment 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 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. The final analysis of the study data will occur once the last escalation phase patient recruited has completed the Final visit after 6 cycles of treatment or when approximately 20 deaths have occurred in the expansion cohort, whichever is the latter. For patients permitted to continue to receive KU-0059436 (and Gemcitabine if applicable) 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. Patients continuing on study therapy (KU-0059436 (and Gemcitabine if applicable) 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.

In addition any known untoward event occurring subsequent to the AE / SAE reporting period that the investigator assesses as possibly related to the study treatment(s) should also be reported as an AE / SAE.

11.4.3 Definition of Relationship of AEs to the Study Drug

The investigator will also be asked to assess the possible relationship between the AE and the KU-0059436 and Gemcitabine. 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 Gemcitabine 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 Gemcitabine.

- 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.

11.4.4 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 12.

Table 12: 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** reaction is not necessarily a **serious** reaction. 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.

11.4.5 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 investigative site staff become 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 the Sponsor's Drug Safety Department, by fax (or e-mail where a dedicated Drug Safety e-mail address is available).

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

The Sponsor's drug 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:

Mail Address:

[redacted]

11.4.6 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 11.4.5.

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.

For all remaining escalation patients receiving KU-0059436 (and Gemcitabine if applicable) after completion of the Final visit following 6 cycles of combination treatment, 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 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 Gemcitabine) 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.

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

All study-related AEs and SAEs must be followed until resolution, unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease or the patient is lost to follow-up. AstraZeneca reserves the right to ask for further information on any AE which may be considered of interest.

11.4.8 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, when required to do so.

AstraZeneca, or its designee, Theradex, will inform investigators of all serious unexpected adverse drug experiences attributed to the use of KU-0059436 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.

12.0 DATA EVALUATION AND ANALYSIS

12.1 Data Collection

All trial 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 may 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 computerized and entered into a master file with appropriate and documented proofreading.

12.3 Population and Type of Analyses

Dose Escalation Phase

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 trial population, the observed anti-neoplastic response and the biologic response. All reported symptoms and adverse events will be coded according to the CTC- MedRA coding system and presented and summarized by dose. Crude incidence rates will be based on the maximum intensity 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.

The following parameters will be derived for KU-0059436 when dosed continuously alone and when dosed together with Gemcitabine: steady state C_{max} (maximum concentration achieved after drug administration), steady state t_{max} (time to C_{max}), steady state AUC_{0-12} (area under the curve across the dosing interval). Since, for patient and investigation site convenience, a PK sample is not being collected at 12 hours after KU-0059436 dosing, the pre-dose concentration value will be used twice in the profile for the purposes of calculating the AUC_{0-12} – once at time zero and once at 12 hours after dosing. For each individual patient, the C_{max} and AUC_{0-12} values obtained following dosing on day –4 (KU-0059436 alone data) will be compared with those obtained on day 8 of cycle 1 (KU-0059436 in combination data) to determine whether Gemcitabine has had any effect on plasma exposure to KU-0059436. For discontinuous dosing cycle 1 days 7 and 8 will be compared.

For Gemcitabine, the following parameters will be derived when dosed alone (day 1 of cycle 1) or in combination with KU-0059436 (day 8 of cycle 1: C_{inf} (concentration at end of infusion, AUC_{0-4} and, if supported by the data, terminal half life, AUC, clearance and volume of distribution. The individual patient parameter values obtained following dosing on day 1 (Gemcitabine alone data) will be compared with those obtained on day 8 of cycle 1 (Gemcitabine in combination data) to determine whether KU-0059436 has had any effect on the plasma pharmacokinetics of Gemcitabine.

Dose expansion Phase

All patients in the expansion part of the study will be included in the analysis of the data.

The objective response rate will be compared between the two treatment groups using Fisher's Exact Test. The objective response rate will be summarised and the 80% and 95% confidence intervals for the difference calculated using the Wilson score based method (Newcombe, RG).

Progression free survival and overall survival will be compared between the two treatment groups using a Cox proportional hazards model with a factor for treatment group. The effect of the combination group relative to Gemcitabine alone will be estimated by the hazard ratio together with its corresponding 80% and 95% confidence intervals. The hazard ratio will be calculated such that a value <1 will

imply the treatment effect is in favour of the combination group. Summary statistics will also include the number of patients, number of events, median time to event and the 25th and 75th percentiles. Kaplan-Meier plots for progression free survival and overall survival will be presented by treatment group.

Descriptive statistics and data listings will be used to describe the trial population, the observed anti-neoplastic response and the biologic response. All reported symptoms and adverse events will be coded according to the CTC- MedRA coding system and presented and summarized by group. Crude incidence rates will be based on the maximum intensity 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.

Analysis of the KU-0059436 plasma concentration data will be carried out using non-linear mixed effects modelling via NONMEM in order to estimate individual patient KU-0059436 exposure, with a view to exploring exposure-response relationships.

12.4 Patient Follow-Up

For patients who withdraw prior to completion of 6 cycles of combination treatment a follow-up is planned for a minimum of 30 days following the last treatment and if possible until progressive disease, and the patient data will be included in the final analyses. Expansion patients will be followed up for survival. If patients have an ongoing Adverse Event considered as suspected, probably related or definitely related to the protocol treatment the patient will be followed until the Adverse Event has either returned to the baseline grade or ≤ grade 1; or, if the AE is determined to be chronic, a cause is identified; or until the patients starts another type of anti-neoplastic therapy or unless in the opinion of the investigator the condition is unlikely to resolve due to the patient's underlying disease.

For all remaining escalation patients permitted to remain on KU-0059436 (and Gemcitabine if applicable) treatment after completion of the Final visit, following 6 cycles of combination treatment, AEs will cease to be reported but documented in the medical notes. All new SAEs occurring on KU-0059436 (and Gemcitabine if applicable) 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 TRIAL MANAGEMENT AND QUALITY CONTROL

13.1 Ethical and Legal Considerations

The trial 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 trials. 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, a completed FDA Form 1572 and a financial disclosure statement to Theradex®. All sub-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 trial. Patients must also be notified that they are free to discontinue from the trial 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 trial. The ICF must be signed and personally dated by the person who conducted the IC discussion. 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 trial 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 trial, including the patient's medical history.

The patient information and informed consent form may need to be revised during the trial 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 trial.

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 study drugs in connection with this Clinical Trial, 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 study drug, KU-0059436, administered to the patient in this Clinical Trial has been supplied by AstraZeneca and that the investigator and his assistants have performed this clinical trial 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 trial 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 trial) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives.

During the trial, 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 trial is conducted according to the guidelines for ICH/GCP,
- confirm that an update of the screening log is performed, and that study drug 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 trial.)

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 trial 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 trial (medical, nursing and other staff). In collaboration with AstraZeneca the investigator will ensure that appropriate training relevant to the trial and/or trial procedures is given to all of these staff, and that any new information of relevance to the performance of this trial is forwarded to the staff involved.

13.8 Sponsorship, Filing and Data Management

AstraZeneca will be sponsoring the trial. Patient data will be registered at the treatment centre. AstraZeneca will supply the treatment centre with all necessary material and case report forms (CRF) at the initiation of the trial. 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 trial documentation, and be filed for at least 2 years after marketing approval ends, and for at least 15 years, in total.

The investigator must arrange for the retention of the patient identification codes, (i.e. hospital/unit code, trial identification code and trial number) for as long as the sponsor requests after completion or discontinuation of the clinical trial. 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 trial, 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 Trial

AstraZeneca will financially support this trial. The company will deliver the KU-0059436 free of charge, as well as paying the investigator a fee for the patients included, which will cover the trial costs. No money will be paid to the patients other than any reasonable travel costs.

13.10 Reporting of the Trial

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

The final clinical report of this trial 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 Trial

The trial 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 trial results will have to be reviewed and approved by AstraZeneca, who has a 30-day period to respond.

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APPENDIX I: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI (1996 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 (not used in this study)
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 cancer and therefore will not be used in this study (however CA15-3 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 therefore 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 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. In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-target lesions	New lesions	Overall 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.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to ensure "symptomatic deterioration" patients continue to have objective tumour assessments at withdrawal from study and until progression is confirmed by imaging.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

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 trials 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 trial 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 study drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring 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 study drug.

1. Time Course. Exposure to suspect study drug. Has the patient actually received the suspect study drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect study drug?
2. Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect study drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
3. Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect study drug?
4. No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or

environmental factors.

5. Rechallenge experience. Did the AE reoccur if the suspect study drug was reintroduced after having been stopped? Rechallenge is not normally recommended or supported.
6. 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 study drug?
- Is there a known mechanism?

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

APPENDIX 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