Clinical Study Protocol

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Date	

A Phase I, Open-Label, Dose-Escalation Study to Assess Safety, Tolerability, and Pharmacokinetics of AZD7762 Administered as a Single Intravenous Agent and in Combination with Weekly Standard Dose Gemcitabine in Japanese Patients with Advanced Solid Malignancies

Sponsor:

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

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

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

PROTOCOL SYNOPSIS

A Phase I, Open-Label, Dose-Escalation Study to Assess Safety, Tolerability, and Pharmacokinetics of AZD7762 Administered as a Single Intravenous Agent and in Combination with Weekly Standard Dose Gemcitabine in Japanese Patients with Advanced Solid Malignancies

Principal Investigator

Study centre(s) and number of subjects planned

This study will be conducted at Approximately 45 patients with advanced solid malignacies will be enrolled in this study, depending on the number of AZD7762 dose escalations required.

Study period		**Phase of development**
Estimated date of first subject enrolled	June 2009	1
Estimated date of last subject completed	July 2013	

Objectives

The primary objective of this study is to assess safety and tolerability of AZD7762 alone and in combination with gemcitabine, by assessment of Common Terminology Criteria Adverse Events version 3.0 (CTCAE) grade and type of adverse events (AEs), changes in laboratory values, vital signs, cardiac markers, ECG and left ventricular ejection fraction (LVEF).

The secondary objectives of the study are:

1. To determine the single-dose PK of AZD7762 when administered alone by assessment of C_{max}, area under the plasma concentration-time curve from zero to infinity (AUC), area under the plasma concentration-time curve to the last quantifiable plasma concentration ($AUC_{(0-t)}$), clearance (CL), half-life associated with terminal slope of a semi-logarithmic concentration-time curve ($t_{½\lambda z}$), mean residence time (MRT), volume of distribution at steady state (V_{ss}), and plasma drug concentration at 24 hours after administration of a given dose (C_{24h})

2. To compare the clearance (CL) of AZD7762 and gemcitabine when given as a single agent to the corresponding CL value when AZD7762 and gemcitabine are given in combination

3. To seek preliminary evidence of the anti-tumor activity of AZD7762 administered in combination with gemcitabine by assessment of Response Evaluation Criteria in Solid Tumors (RECIST)

The exploratory objectives of the study are:

1. To explore the relationship between p53 and MDM2 tumor expression (and other genes/proteins implicated in the cell cycle) and clinical response

2. Optional: In consenting patients, to obtain a blood sample for DNA extraction for retrospective pharmacogenetic analysis

Study design

This is an open-label, dose-escalation, Phase I study to evaluate the safety, tolerability, pharmacokinetics and tumor response when AZD7762 is administered alone and in combination with gemcitabine.

Target subject population

Japanese patients with advanced solid malignancies for whom single agent weekly standard dose of gemcitabine therapy is considered appropriate

Investigational product, dosage and mode of administration

Gemcitabine will be administered as a 30-minute IV infusion. AZD7762 will be administered as a 60-minute IV infusion immediately upon completion of gemcitabine infusion. The starting dose of AZD7762 will be 6 mg. A dose of AZD7762 in the next patient cohort will be selected based on the available safety and PK data from all evaluable patients in this study and the overseas study (see Section 4.1.3). The dose of gemcitabine will be a full standard dose of 1000 mg/m^2 and will be adjusted according to label and standard local practice(see Section 6.4.4.3).

Patients will receive a single dose of AZD7762 2 doses at a one week interval (Cycle 0). After the confirmation of patients' safety during Cycle 0, patients will receive AZD7762 in combination with gemcitabine 2 doses at a one week interval followed by a rest week (Schedule A, 1 cycle=3 weeks). Dose escalation will proceed with Schedule A. Dose escalation will proceed until any of the defined stopping criteria is met (see Section 4.1.5).

Once the MTD is established in Schedule A, two cohorts will be evaluated for safety and tolerability of the study treatment using 3 consecutive doses given at one week interval followed by a rest week (Schedule B, 1 cycle=4 weeks). The first cohort will receive AZD7762 at one dose lower than the AZD7762 MTD determined in Schedule A combined with full dose chemotherapy. If this is safe and tolerable the second cohort will receive the

MTD of AZD7762 from dose escalation phase and full dose chemotherapy. In addition, after determination of safe and tolerable dose of AZD7762 in Schedule B, three more patients will be incorporated into that cohort to study the effect of AZD7762 on the pharmacokinetics (PK) of gemicitabine (the "PK expansion group"). Cycle 0 will be omitted for the patients in Schedule B and the "PK expansion group". For the patients in the "PK expansion group", only gemcitabine will be administered to on Cycle 1, Day 1, AZD7762 will be administered from Cycle 1, Day 8..

Duration of treatment

Following the completion of Cycles 0 and 1, individual patients may continue treatment indefinitely after giving consent to the continued study treatment, provided that in the opinion of the Investigator: (a) they are continuing to benefit, (b) there is no evidence of disease progression, and (c) they do not meet any other withdrawal criteria..

Outcome variable(s):

- Safety

  CTCAE v. 3.0 grade and type of adverse events (AEs), changes in vital signs including blood pressure (BP), pulse, body temperature, changes in laboratory findings (including clinical chemistry, hematology, and urinalysis), cardiac markers (quantitative and qualitative troponin T), and changes in left ventricular ejection fraction (LVEF) by echocardiogram (ECHO)

- Efficacy

  Objective tumor response using RECIST

- Pharmacokinetics

  The following PK parameters of AZD7762 will be calculated based on the plasma concentration time profile obtained following a single dose on Cycle 0, Day 1 (AZD7762 alone) and Cycle 1, Day 8 (gemcitabine and AZD7762 combination): C_{max}, C_{24h}, AUC, $AUC_{(0-t)}$, CL, $t_{½\lambda z}$, MRT and V_{ss}

  The following PK parameters of gemcitabine will be calculated based on the plasma concentration time profile obtained following a single dose on Cycle 1, Day 1 (gemcitabine alone) and Cycle 1, Day 8 (gemcitabine and AZD7762 combination): C_{max}, AUC, $AUC_{(0-t)}$, CL, $t_{½\lambda z}$, MRT and V_{ss} (the "PK expansion group" only).

Statistical methods

All safety, tolerability and PK data will be summarized using descriptive statistics and exploratory graphical presentations of the data. All summaries will be presented by dose, cycle and dosing schedule (ie, Schedule A or B [patients in the "PK expansion group" will be included in Schedule B]).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
5-HT_{2B}	5-hydroxytryptamine-2B
5-HT_{2C}	5-hydroxytryptamine-2C
AAG	α1-acid glycoprotein
ADME	Absorption/Distribution/Metabolism/Excretion
AE	Adverse event (see definition in Section 7.3.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATM	Ataxia-telangiectasia mutated
ATP	Adenosine 5'-triphosphate
ATR	Ataxia-telangiectasia and RAD3-related
AUC	Area under the plasma concentration-time curve from zero to infinity
$AUC_{(0-t)}$	Area under the plasma concentration-time curve to the last quantifiable plasma concentration
$AUC_{(0-48h)}$	Area under plasma concentration-time curve from zero to 48 hours
AUMC	Area under plasma first moment concentration-time curve [amount· $time^2$/volume]
BED	Biologically Effective Dose
BNP	Natriuretic brain peptide
BP	Blood pressure
BUN	Blood urea nitrogen
C_{24h}	Plasma drug concentration at 24 hours after administration of a given dose
Chk	Checkpoint kinase
CL	Total body clearance of drug from plasma
C_{max}	Maximum plasma (peak) drug concentration after single dose administration
CNS	Central nervous system

Abbreviation or special term	Explanation
CPK	Creatine phosphkinase
CR	Complete response
CRF	Case Report Form (electronic/paper)
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events version 3.0-
CYP	Cytochrome P450 enzyme system
DAE	Discontinuation due to Adverse Event
DBL	Data base lock
dFdCDP	Gemcitabine-diphosphate
dFdCTP	Gemcitabine-triphosphate
dFdU	2'-deoxy-2',2'-difluorouridine
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
ECHO	Echocardiogram
EC_{50}	Concentration giving 50% of the drug-induced effect (response) [amount/volume]. Also called potency.
ECG	Electrocardiogram
ED_{50}	Effective dose 50%
ED_{100}	Effective dose 100%
EF	Ejection fraction
EPO	Epoetin
FOB	Functional observation battery
FTIM	First time in man
G1 phase	Gap 1 phase
G2 phase	Gap 2 phase
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factors
GI_{50}	Concentration of drug causing 50% growth inhibition
GLDH	Glutamate dehydrogenase
GSH	Glutathione
Hb	Haemoglobin
HCG	Human chorionic gonadotrophin

Abbreviation or special term	Explanation
HCT	Hematocrit
HIV	Human immunodeficiency virus
HR	Heart rate
IC_{50}	Inhibitory concentration 50%
ICH	International Conference on Harmonization
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenously
K_i	Inhibitory constant
LCK	Log cell kill
LVEF	Left ventricular ejection fraction
MCV	Mean corpuscular volume
MDM2	A gene involved in the regulation of p53
MI	Myocardial infarction
M-phase	Mitotic phase
MRT	Mean residence time
MTD	Maximum tolerated dose
NOEL	No effect level
NYHA	New York Heart Association
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 7.3.1
p53	Tumor suppressor protein p53
pChk1	Phosphorylated checkpoint kinase 1
PD	Pharmacodynamic
Pgp	p-glycoprotein
PK	Pharmacokinetic
PLT	Platelet count
PR	Partial response
RBC	Red Blood Count
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event (see definition in Section 7.3.2).

Abbreviation or special term	Explanation
SAP	Statistical analysis plan
S-phase	DNA synthesis
STD	Serious toxicity dose
$t_{1/2}$	Half-life
$t_{1/2\lambda z}$	Half-life associated with terminal slope (λ_z) of a semi-logarithmic concentration-time curve
ULN	Upper limit of normal
ULRR	Upper limit of reference range
V_d	Volume of distribution
V_{ss}	Volume of distribution at steady state
WBC	White blood cells
WHO	World Health Organization

1. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

1.1 Medical emergencies and AstraZeneca contacts

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 7.3.4**

In the case of a medical emergency you may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site shown below.

Name	Role in the study	Address & telephone number
	Study Delivery Team Leader	
	Study Delivery Team Physician	

1.2 Overdose

There is currently no known antidote to AZD7762. The treatment of AEs associated with overdose should be supportive for the underlying symptoms. Doses of study treatment in excess of that specified in the clinical study protocol are considered to be an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

1.3 Pregnancy

All outcomes of pregnancy must be reported to AstraZeneca.

1.3.1 Maternal exposure

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the subject is immediately withdrawn from the study and investigators or other site personnel inform appropriate AstraZeneca representatives immediately but no later than the end of the next business day of when he or she becomes aware of it.

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

1.3.2 Paternal exposure

The outcomes of any conception occurring from the date of the first dose until a 6 months following the last dose must be followed up and documented.

Male patients must refrain from fathering a child during the study and 6 months following the last dose, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated

Pregnancy of the subjects partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

2. INTRODUCTION

2.1 Background

The majority of clinically effective anticancer chemotherapeutic agents achieve their pharmacologic effects by relatively non-selective deoxyribonucleic acid (DNA) damage of both tumor and normal tissue cells. The DNA damage involves single and double strand breaks as well as interference with the function of DNA replication forks (replication stress). DNA damage typically evokes cellular responses to allow cell repair. A well-described key component of repair is the activation of two checkpoint kinases (Chk1 and Chk2).

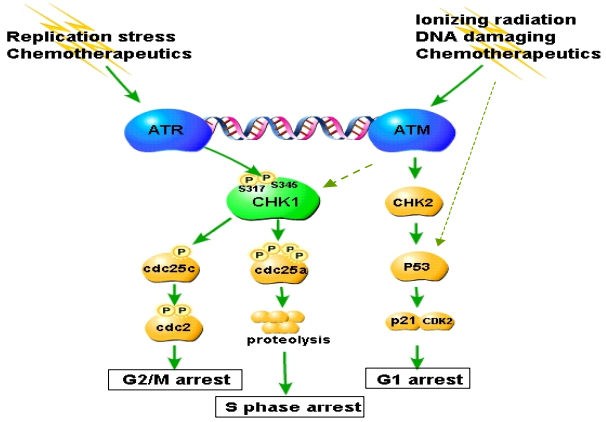
To survive, a cell must accurately replicate its genome and activate appropriate repair pathways if DNA is either not fully replicated or damage is detected. If DNA is damaged, the cell cycle is delayed to allow DNA repair prior to cell division. While cell cycle delay is protective for normal cells, it also can reduce the effectiveness of many cancer therapies. If a checkpoint-mediated cell cycle arrest and DNA repair could be selectively reduced in tumor

cells but not in normal cells, tumor cell mitotic catastrophe and death would be enhanced. Normal cells with intact additional checkpoints would be predicted to undergo less cell death.

Chk1 is a kinase in mammals that is involved in the regulation of S and G2-M-phase cell-cycle checkpoints (see Figure 1). Chk1 is a serine/threonine kinase that is activated by ataxia-telangiectasia and RAD3-related (ATR) and/or ataxia-telangiectasia mutated (ATM) by phosphorylation in response to DNA damage (Sanchez et al 1997 and Liu et al 2000). Inhibition of Chk1 kinase activity has been shown to impair cell cycle arrest, and result in increased tumor cell death, particularly in the absence of intact G1 (Gap 1) checkpoint, from loss of tumor suppressor protein p53 (p53) and other oncogenic changes. Normal tissues, however, have a functioning G1 checkpoint-signalling pathway allowing for DNA repair and cell survival. There is increasing evidence from pre-clinical data to suggest that targeting specific cell cycle regulatory enzymes such as checkpoint kinase 1 will selectively induce apoptosis in tumor cells that lack the relevant checkpoint pathways to respond to insult such as DNA damage, while normal cells will simply arrest cell cycle progression during the repair process (Zhao et al 2002, Chen et al 2003, Tenzer et al 2003, Tse and Schwartz 2004, and Zhou et al 2004). Therefore, Chk1 represents an 'Achilles heel' for tumors with deficiencies in these checkpoint pathways, enabling selective potentiation of a DNA-damaging agent's effects against the tumor cells over normal cells.

AZD7762 is a potent, novel and relatively selective inhibitor of Chk1 and Chk2 kinases that binds reversibly in the Chk1 adenosine 5'-triphosphate (ATP) binding pocket and inactivates Chk1 (inhibitory constant (Ki) = 3.6 nM; <10 fold selectivity over a limited number of kinases). The kinases showing less than 5 fold selectivity include several Src family members (eg, Fgr, Fyn, Lck and Lyn, but not Src), Flt1/3, CSF1R, Ret and Abl. Chk2 showed very modest activation as measured by Chk2 phosphorylation following gemcitabine or irinotecan treatment in tumor cell lines as compared to Chk1. Therefore, the relevance of AZD7762 driven Chk2 inhibitory activity in cells is uncertain. *In vitro* and *in vivo* profiling has demonstrated increases in the delay to tumor progression and cytotoxic response to DNA-damaging agents in multiple cell lines with the addition of AZD7762 compared to DNA-damaging agents alone, supporting the potential broad utility of AZD7762 in combination with DNA-damaging chemotherapy. Although no histopathology was done, in the pre-clinical efficacy studies, no overt increase in toxicity was observed with the addition of AZD7762 to single agent chemotherapy supporting lack of significant increased toxicity with the combination. The clinical program for AZD7762 focuses on combination therapy with potent DNA-damaging agents known to activate Chk1 in tumors, and whose activities have been demonstrated to be significantly enhanced in pre-clinical studies, such as gemcitabine.

Figure 1 DNA-damage response pathway



2.2 Non-clinical experience

2.2.1 Non-clinical pharmacology

The principal findings are summarised below:

Primary pharmacodynamics

- AZD7762 is a potent inhibitor of Chk1 that binds in the ATP binding pocket with a 50% inhibition concentration (IC_{50}) of 5 nM and an inhibitory constant (K_i) of 3.6 nM.

- AZD7762 had activity in a range of other kinases. Examples of kinases with a <5-fold selectivity included Rous sarcoma oncogene cellular homolog (SRC) family members (eg, Fgr, Fyn, lymphocyte-specific protein-tyrosine kinase [Lck], and Lyn, but not SRC), colony stimulating factor receptor [CSF1R], RET, Abelson tyrosine kinase [Abl], and checkpoint kinase 2 [Chk2]. It is not known if the in vitro kinase inhibition translates into an in vivo effect.

- In combination with DNA-damaging agents (gemcitabine, topotecan, doxorubicin, and cisplatin), AZD7762 inhibits tumour cell growth in vitro with a mode of action that correlates with Chk1 inhibition and abrogation of the Gap 2 (G2) and S phase checkpoints. Fold-shifts in 50% growth inhibition (GI_{50}) values over DNA-damaging agents alone ranged from 9- to 22-fold with gemcitabine demonstrating the largest shifts followed by topotecan.

- In combination with radiation, AZD7762 enhances tumour cell growth inhibition and death with survival enhancement ratios ranging from 1.7 to 1.9. Triple combinations with AZD7762, gemcitabine, and radiation yield the largest survival enhancement ratios.

- Differential sensitivity between isogenic cancer cells with defects in p53 as compared to p53 wild type was observed in combination with topotecan, doxorubicin, gemcitabine, and radiation. Other checkpoint or repair mutations not tested could also drive a differential in sensitivity.

- Exploratory studies suggest ex vivo treatment of purified CLL tumour cells with single agent AZD7762 leads to increased tumour cell death over control in a subset of samples derived from fludarabine-refractory patients.

- AZD7762 was active in the pharmacodynamic (PD) in vivo assay where inhibition of Chk1 resulted in the abrogation of DNA-damage-induced cell cycle arrest. A clear pharmacokinetic (PK)/PD relationship has been established.

  - In vitro washout studies showed that exposure to AZD7762 for more than 8 hours (h) above the 50% effective concentration (EC_{50}) was required for optimal checkpoint abrogation.

  - In vivo studies established that exposure time proportionally correlates with PD activity, and that exposure for a least 8 h above EC_{50} was required for maximum PD activity. In the rat PD model, the doses giving 50% of the drug-induced effect (ED_{50}) and 100% of the drug-induced effect (ED_{100}) were 15 mg/m^2 (2.5 mg/kg) and 30 mg/m^2 (5 mg/kg), respectively.

- AZD7762 potentiated DNA-damage-mediated tumour cell death in a number of human tumour xenograft models the extent of which depends on the cell line and DNA-damaging agent used. Potentiation is observed in combination with gemcitabine, resulting in a significant (0.9 log cell kill [LCK]) increase in anti-tumour activity. Importantly, the efficacy of gemcitabine is enhanced in both gemcitabine-sensitive as well as relatively insensitive human tumour models in combination with AZD7762. Furthermore, increased efficacy is achieved without impacting the tolerability or maximum tolerated dose (MTD) of gemcitabine and irinotecan in rat models. Tumour free survival is achieved in a colorectal xenograft model in mouse when AZD7762 is delivered in combination with irinotecan at the mouse MTD.

Safety and secondary pharmacology

- The activity of AZD7762 was tested in vitro against a panel of receptor and enzyme binding assays and showed binding to adenosine A1, α2A-adrenoceptor, L-type calcium channels (benzothiazepine and phenylalkylamine), sodium channel, imidazoline I2, 5-hydroxytryptamine receptors [5-HT2B and 5-HT2C].

- Findings in rats and dogs in vivo were consistent with a dose-related decrease in cardiac contractility.

In conscious rats, AZD7762 at doses 196-391 mg/m^2 (90-180 μmol/kg) produced a hypotensive effect associated with bradycardia, decreased core temperature, and a respiratory depressant effect.

In conscious telemetered dogs, decreases in contractility and blood pressure were seen, but were not sustained and were completely reversible within 4 h. At 5 and 152 mg/m^2 (0.75 and 21 μmol/kg) cardiac contractility was 22% and 34% of that in controls at the end of 1-hour infusion.

In anaesthetised dogs, 11-362 mg/m^2 (1.5-50 μmol/kg) AZD7762 produced a dose-related decrease in cardiac contractility with a concomitant fall in blood pressure. At 72 mg/m^2 (10 μmol/kg) and above, suppression of these parameters was sustained to the point that the dogs were unable to maintain homeostasis and either died or were terminated. Measured exposures in PK studies were 2- to 5-fold higher than those achieved in conscious animals at similar doses. AZD7762 at 5 mg/m^2 (0.75 μmol/kg) had no effect on cardiovascular function.

- Given the increased sensitivity of the anaesthetised model, additional studies were conducted to explore possible mechanisms of haemodynamic changes and the effect of AZD7762 when combined with opiate analgesics.

  In vitro studies demonstrated that AZD7762 was not an agonist or antagonist of the adenosine A1 receptor and was not an effective inhibitor of L-type calcium channels. Consequently, the mechanisms underlying the negative inotropic changes remain unknown.

  There was no evidence of any potentiation of the effects of AZD7762 by opiates. Co-treatment of rats with AZD7762 and morphine did not enhance the effects on heart rate, blood pressure, or respiratory effects.

- AZD7762 from 5 mg/m^2 (0.75 μmol/kg) to 362 mg/m^2 (50 μmol/kg) produced increases in PR interval in dogs (up to 23%) that were dose-related and completely reversible within 1 hours.

- In the rat functional observational battery (FOB), doses up to 217 mg/m^2 (100 μmol/kg) had minor effects on body temperature and body weight at the high dose.

- In the respiratory function study in rats, AZD7762 had a slight respiratory depressant effect at 326 mg/m^2 (150 μmol/kg) only.

In vitro and in vivo, abrogation of DNA damage-induced cell cycle arrest and a clear relationship between drug exposure and checkpoint abrogation was established resulting in a good PK/PD relationship being demonstrated. Extrapolating to human exposure, sustained concentrations associated with PD activity with an ED_{50} to ED_{100} for abrogation of the Chk pathway at doses of 15 to 30 mg/m^2 (approximate doses of 27 to 54 mg). Preclinical

modelling utilizing both PD and efficacy models predicts the estimated biological dose to range from 50-60 mg.

2.2.2 Pharmacokinetics and drug metabolism in animals

Non-clinical metabolic disposition and pharmacokinetic studies have been conducted in rat and dog, the species used for the toxicology studies. AZD7762 has also been used in supportive in-vitro studies designed to determine plasma protein binding, cross-species metabolism, and interaction with cytochrome P450 (CYP) enzymes. Key findings are as follows:

- AZD7762 showed peak plasma concentrations (C_{max}) of 1.76 µmol/L in rats at a dose of 43 mg/m^2 (20µmol/kg) and 1.12 µmol/L in dogs at a dose of 36 mg/m^2 (5 µmol/kg) at the end of infusion, which fell rapidly thereafter.

- In both rat and dog, there was a large volume of distribution (V_d) and a high clearance (CL) resulting in a short half-life ($t_{1/2}$; ~2 h in the rat and 5-6 h in the dog).

- Exposure to AZD7762 increased in a greater than dose proportional manner in the rat and dog; the nonlinearity in the dog on Day 1 was less marked than the rat. No changes in exposure were observed in the dog following 3 doses of AZD7762 on a weekly dosing schedule; a slight decrease in exposure was observed in the rat on Day 15/16 at 326 mg/m^2 (150 µmol/kg) of AZD7762.

- AZD7762 was moderately bound (84-89%) to plasma proteins of mouse, rat, rabbit, dog, and man. AZD7762 was principally bound to human serum albumin (HSA) (70%), which was unaffected by concentration; binding to α1-acid glycoprotein (AAG) was reduced at higher concentrations. Drug-related material was rapidly and extensively distributed throughout the rat with only low levels in the central nervous system (CNS) and male and female sex organs.

- Studies with rat, dog and human hepatocytes demonstrated a large species difference in the metabolism of AZD7762 - metabolism was extensive in the rat, moderate in the dog, and undetected in the human. The major metabolite in the rat was a glutathione (GSH) conjugate of defluoro-hydroxy AZD7762. Other metabolites included a cysteine conjugate of defluoro-hydroxy AZD7762 together with oxygenated AZD7762 and its sulphate and glucuronide conjugates. Incubations with trapping reagents showed the formation of at least three reactive intermediates using rat microsomes - one of these was seen with human microsomes but was only a very minor component.

- Investigation into the metabolism of [^{14}C]-AZD7762 in rat and dog showed that, with the exception of rat bile, the major component detected in all samples examined was AZD7762. Minor species or gender differences were observed in the metabolite profiles of plasma, urine or faeces.

- The major component in rat (1-3 h) and dog plasma (1-5 h) was AZD7762, with a minor unidentified component detected in both species.

- In rat bile (0-6 h), AZD7762 was extensively metabolised accounting for <2% dose. Eight components were identified in bile, the major one of which was desfluoro-hydroxy cysteine metabolite of AZD7762 (M4: 16%). Other minor metabolites of AZD7762 included a mono-oxygenated glucuronide/or glycylcysteine, a mono-oxygenated glucuronide (M3: 3.3%), a desfluoro-hydroxy glutathione (M5: 3.6%), a desfluoro-hydroxy mercapturic acid (M6: 2.7%), mono-oxygenated (M7: 5.6%) and its sulphate derivative (M9: 2.1%).

- The metabolite profiles in rat and dog excreta were qualitatively similar, with up to 6 components detected. The major component, detected in both species, was unchanged AZD7762 (37-50% dose). Mono-oxygenated AZD7762 was the major faecal metabolite in rat (M7: 12%) and dog (M8: 8%), possibly existing in different isomeric forms. In urine, the major component was AZD7762 (7-10% dose). Desfluoro-hydroxy cysteine AZD7762 (M4: <2%) was detected in both species, with two additional minor components (M6: trace and M7: 0.6%) found only in rat urine.

- Following an IV infusion to rats and dogs over 1 h, radioactivity was predominantly excreted in faeces (>60%), with urine representing a relatively minor route of elimination (approximately 15%). The rate of elimination in both species was rapid (majority recovered within 48 h) and recovery was essentially complete by 7 days.

- AZD7762 is a weak inhibitor of the cytochrome P450 enzyme 1A2 (CYP1A2; IC_{50} value of 157 μM; K_i=78.5 μM) and is a more potent inhibitor of CYP2C8 (IC_{50} value of 2.23 μM; K_i=1.12 μM). AZD7762 is not a mechanism-based inhibitor of CYPs 2C8, 2C9 or 3A4.

- AZD7762 was a substrate for the efflux protein p-glycoprotein (Pgp) but did not inhibit transport of the standard Pgp substrate digoxin. AZD7762 inhibited the growth of the parental MCF7 and Pgp-expressing MCF7-matched cell line to the same magnitude (IC_{50}=0.24 and 0.34, respectively).

2.2.3 Toxicology

Key toxicology findings are as follows.

- Acute lethality occurred in rats given AZD7762 intravenously at 391 mg/m^2 (180 μmol/kg). Dose limiting toxicity (DLT) occurred in the dog at 362 mg/m^2 (50 μmol/kg) and included decreased activity, irregular respiration, lachrymation, ataxia, and histological changes involving the haematopoietic and gastrointestinal systems with haemorrhage and infection due to haematopoietic dysfunction.

- Minimal to mild ventricular myocarditis was observed (particularly in males) in a minority of rats given a 1-h IV infusion of AZD7762 at 43 to 326 mg/m^2 (20-150 μmol/kg). While the overall incidence of myocarditis was 1 in 6 (ie, 10 of 60), 9 were seen in males (n=30), and only 1 in females. An investigative study showed that after a single dose of AZD7762 at 326 mg/m^2 (150 μmol/kg), a rise in troponin T, was evident after 2 hours and AST, creatine kinase and myoglobin within 4 hours of dosing.

- Plasma liver enzymes (ALT, ALP, AST and GLDH) were elevated in a number of studies in rats and dogs suggestive of a potential effect on the liver, however, no histopathological correlate was seen. Effects on haematopoietic parameters (eg, decreased white and red blood cell indices and reticulocytes) were also noted.

- AZD7762 was not mutagenic in vitro, but was positive in a rat micronucleus study.

An in vitro blood compatibility assay showed potential for AZD7762 to cause erythrocyte clumping at concentrations of 6.25 and 12.5 μmol/mL, and plasma precipitation at 0.12-3.75 μmol/mL. AZD7762 did not cause irritation of perivascular tissue in the mouse perivenous study, although scabs and discoloration at the infusion site were occasionally seen. No evidence of haemolysis or blood compatibility issues have been seen in vivo.

2.3 Pharmacokinetic background

2.3.1 Drug-drug interactions

There appears to be limited potential for drug-drug interactions based on the in vitro studies performed with Cytochrome P450 enzymes. AZD7762 is a weak inhibitor of CYP1A2 (IC_{50} value of 157 μM; K_i = 78.5 μM) and is a more potent inhibitor of CYP2C8 (IC_{50} value of 2.23 μM; K_i = 1.12 μM) – this may have implications if AZD7762 is co-administered with drugs that are metabolised by this enzyme (eg, taxanes). Although AZD7762 is a substrate for P-glycoprotein-mediated efflux, which may explain its limited distribution into the CNS, it does show activity in tumors that express Pgp. AZD7762 did not inhibit the transport of digoxin, a known Pgp substrate.

2.3.2 Gemcitabine PK data in man

See the package insert for an overview of the PK of single agent gemcitabine.

2.3.3 Potential for PK interaction between AZD7762 and gemcitabine

No formal pre-clinical PK data in animals exists examining the interaction between gemcitabine and AZD7762. However, the difference in distribution and capacity of elimination pathways makes it impractical to use interaction PK data from animal models. Based on the available pre-clinical PK data for AZD7762, the potential for AZD7762 to affect the PK of gemcitabine is probably low. Gemcitabine has not been shown to significantly modulate well-characterized drug metabolizing pathways, thus the potential effect of gemcitabine on the PK of AZD7762 is likely to be minimal. Notwithstanding, to mitigate the potential effect of gemcitabine unexpectedly inhibiting the metabolism of AZD7762 and

resulting in unacceptable toxicity, the dose of AZD7762 will be gradually escalated using predetermined safety and PK criteria (refer to Section 4.1.2).

2.4 Clinical experience

At this time, 2 separate Phase I trials (Study D1040C00002 and Study D1040C00004) are underway, both, as of 9 March 2009 are currently in the dose escalation phase:

- **Study D1040C00002** is a Phase I open-label multicenter dose escalation study to assess the safety, tolerability and pharmacokinetics of AZD7762 when administered as a single, intravenous agent and in combination with weekly standard dose gemcitabine in patients with advanced solid malignancies.

- **Study D1040C00004** is a Phase I open-label multicenter dose escalation study to assess the safety, tolerability and pharmacokinetics of AZD7762 when administered as a single, intravenous agent and in combination with weekly standard dose irinotecan in patients with advanced solid malignancies.

In each study, the treatment schedule is as follows: 2 weekly doses of single agent AZD7762 ("cycle 0") preceding 2 weekly doses of AZD7762 in combination ("cycle 1") with weekly gemcitabine (Study D1040C00002) or irinotecan (Study D1040C00004) in three-week cycles. The starting dose of AZD7762 was identical (6 mg) for the first 2 dose levels, with single-agent chemotherapy reduced at the first dose level (75% [gemcitabine] or 80% [irinotecan]of the standard dose) and increased to a full dose at second dose level. Both studies include multiple parts: a dose escalation phase to determine the Maximum Tolerated Dose (MTD) and during which the estimated Biologically Effective Dose (BED) will be identified; and a dose expansion phase to gather preliminary information on anti-tumour activity in patients given the MTD (or other dose selected from the escalation phase) in combination with gemcitabine (Study D1040C00002) or irinotecan (Study D1040C00004).

As of 9 March 2009 (preliminary and unvalidated), both studies are still in the dose escalation phase. Study D1040C00002 has evaluated 6 levels up to and including a 32 mg dose of AZD7762 and Study D1040C00004 has evaluated 5 dose levels inclusive of the 21 mg dose. A total of 50 patients have been treated in these 2 companion AZD7762 clinical trials; 25 in Study D1040C00002 and 25 in D1040C00004. One patient in D1040C00002 Cohort 6 (32 mg AZD7762 / 1000 mg/m^2 gemcitabine) with ocular melanoma, metastatic disease to the liver and lung, and grade 1 cisplatin-induced neuropathy, experienced Grade 3 sensory neuropathy in the left arm during Cycle 0 that resolved following treatment with steroids and narcotics. The Grade 3 neuropathy was not related to disease or study medication and determined to be related to the patient's pre-existing condition of both cervical disc protrusion and cisplatin-induced neuropathy. The patient was re-challenged with study medication and did not experience a recurrence of neuropathy. During Cycle 1 the patient did experience Grade 4 LFT's (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) at the time the patient discontinued treatment due to progressive disease. One patient in Cohort 4 (14 mg AZD7762 / 100 mg/m^2 irinotecan) experienced a DLT of Grade 3 LFTs (ALT/AST) in Study D1040C00004.

All data presented in Sections 2.4.1 to 2.4.4 are preliminary and unvalidated, and represent data available as of 30 November 2008.

2.4.1 Most common adverse events

The most commonly reported adverse events of any CTCAE grade (reported in at least 3 patients) in Study D1040C00002 were constipation (4 patients), fatigue(4 patients), dehydration (3 patients), and nausea (3 patients). The most commonly reported adverse events of any CTCAE grade (reported in at least 3 patients) in Study D1040C00004 were anorexia (4 patients), diarrhea (4 patients), and fatigue (3 patients).

2.4.2 Dose limiting toxicities (DLTs)

One patient in Cohort 4 (14 mg AZD7762 / 100 mg/m^2 irinotecan) experienced a DLT of Grade 3 ALT in Study D1040C00004.

Two patients treated at the first dose level had a DLT as defined by the protocol due to Grade 3 declines in hemoglobin values in Study D1040C00002. While these 2 events met the protocol-defined DLT criteria, a review of the projected vs actual blood volumes obtained for safety and pharmacokinetic studies showed that, in both patients, the hemoglobin declines could be accounted for by the unanticipated significantly larger than predicted blood volume withdrawn rather than hemolysis or bleeding.

Cardiac events that met protocol-defined DLT criteria were of no known clinical significance, reflected a high degree of sensitivity of a single measure (ultra troponin I level), and a lack of discriminatory ability for difference observed in echocardiogram reading change. These cardiac DLT criteria were subsequently revised, and no cardiac events, either prior to or after the revision have met the new DLT criteria.

2.4.3 Deaths

As of 30 November 2008, there was one death (endocarditis) due to an event not directly due to disease progression in Study D1040C00002, and no fatal events in Study D1040C00004.

2.4.4 Serious adverse events

Of 41 patients who had received at least one dose of AZD7762 as of 30 November 2008, 7 patients (17%) had reported serious adverse events (SAEs) with the use of AZD7762 alone or in combination with chemotherapy. One SAE (endocarditis) in a patient receiving AZD7762 and gemcitabine resulted in death, and 3 SAEs (dehydration, anorexia and diarrhea; all in the same patient receiving AZD7762 and irinotecan) were considered by the investigator to be drug-related. No SAE preferred term was reported by more than one patient.

2.5 Research hypothesis (Not applicable)

2.6 Rationale for conducting this study

DNA-damaging agents remain a cornerstone of anticancer therapy. Although responses and anti-tumor activity are apparent, relapse is commonly the rule rather than the exception. An

agent which could increase the activity of standard DNA-damaging anticancer treatments used in combination with multiple agents in a variety of clinical settings could have great value in the clinic. AZD7762 has shown robust chemo-sensitizing activity with a variety of DNA-damaging agents (including gemcitabine and irinotecan) in pre-clinical studies. Thus, it is expected that combination therapy with AZD7762 and a DNA-damaging anticancer agent, like gemcitabine, may improve the clinical outcome of therapy.

This study will be the first time AZD7762 is administered to Japanese patient. Safety, tolerability and PK data in this Phase I study will support the determination of the dose(s) of AZD7762 to be evaluated in future studies.

This study is designed to provide single agent AZD7762 safety, tolerability and PK data. It will also provide safety, tolerability, pharmacokinetics and tumor response data in combination with gemcitabine. Since all AEs in pre-clinical species were evident in the first week and AZD7762 is intended to be dosed weekly with gemcitabine, in this study AZD7762 will be administered on two successive weeks as a single agent (followed by a 7-day observation period after the second dose); subsequently AZD7762 will be administered following gemcitabine. In this study, two treatment schedules will be evaluated, i.e. Schedule A: once weekly for 2 weeks followed by a rest week, and Schedule B: once weekly for 3 weeks followed by a rest week. Dose escalation will proceed based on the safety and tolerability data from all evaluable patients treated with Schedule A until dose limiting toxicity (≥2 patients) or the pharmacokinetically defined endpoint or MTD defined in preceding overseas study is reached. After confirmation of safety and tolerability of Schedule A, safety and tolerability of Schedule B will be evaluated at MTD and one lower dose level of that in Schedule A.

See Section 4.2 for further detailed description of rationale.

2.6.1 Rationale for analysis of archival tumor sample

There is increasing evidence from pre-clinical data to suggest that targeting specific cell cycle regulatory enzymes such as checkpoint kinase 1 will selectively induce apoptosis in tumor cells that lack the relevant checkpoint pathways to respond to insult such as DNA damage, while normal cells will simply arrest cell cycle progression during the repair process (Zhao et al 2002, Chen et al 2003, Tenzer et al 2003 and Zhou et al 2004). Indeed, inhibition of Chk1 kinase activity has been shown to impair cell cycle arrest, and result in increased tumor cell death, particularly in the absence of an intact G1 checkpoint, either from loss of p53 or other oncogenic changes. As the absence of normal p53 (complete abrogation or presence of mutated form) may further enhance the degree of potentiation obtained from the combination of AZD7762 with DNA-damaging agents, analysis of p53 (and one of the transcriptionally regulated targets of p53, MDM2), may provide invaluable information about the response to AZD7762.

2.6.2 Rationale for genetic analyses

AstraZeneca intends to perform genetic research as part of the AZD7762 clinical development program to explore how genetic variations in germline DNA and somatic mutations in tumor

DNA may affect the clinical outcome parameters observed with AZD7762 and agents used in combination.

Exploration of the associations between gene polymorphisms and other study parameters, such as PK and clinical outcomes could provide several benefits. These include elucidation of which patient populations might benefit most from the drug, and also prediction of potential adverse reactions related to drug exposure.

The analysis of tumor-derived DNA for somatic mutations/genetic alterations is of particular importance. In archived specimens of tumor, evaluation of genes in DNA damage and repair pathways, such as Chk1, Chk2, p53 & p21 may be undertaken. Additional genes implicated in the cell cycle pathway, such as Chk1, Chk2 and p21 may also be investigated within the tumor DNA samples. It is likely that additional information on other genes important for this drug and its response will become available in the future. It is, therefore important to retain the possibility of investigating additional genes, within the tumor samples, in the context of this AZD7762 clinical study.

In addition, analysis of germline genetic material, derived from a blood sample, may be analyzed (optional consent). Genes that may be investigated include those which may be of relevance to the absorption/distribution/metabolism/excretion (ADME) of AZD7762 and/or gemcitabine or those that may influence response to these agents.

2.6.3 Gemcitabine

Gemcitabine is a deoxycytidine (nucleoside) analogue. Following intracellular uptake, gemcitabine is metabolized by nucleoside kinases to two active metabolites, gemcitabine-diphosphate (dFdCDP) and gemcitabine-triphosphate (dFdCTP) nucleosides. Cytotoxicity is attributed mainly to a combination of two actions of the diphosphate and the triphosphate nucleosides, resulting in termination of DNA chain elongation, DNA fragmentation, and cell death. Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary.

Numerous studies have demonstrated the safety and broad anti-tumor activity of gemcitabine when used alone or in combination with other drugs. In the United States, gemcitabine is approved for the treatment of locally advanced (non resectable Stage II or Stage III) and metastatic (Stage IV) adenocarcinoma of the pancreas. It is indicated for patients previously treated with 5-FU. Gemcitabine is also indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer. In Japan, gemcitabine is approved for the treatment of non-small cell lung cancer, pancreatic cancer, biliary tract cancer and urothelial cancer.

Myelosuppression is the principal dose-limiting toxicity with single agent gemcitabine therapy. In single agent studies, grade 3 neutropenia was observed in 19% of patients, and grade 4 neutropenia in 6 to 7%. Neutropenia complicated by infection has been observed in 6% of patients. Grade 3 to 4 thrombocytopenia is less frequent (5 to 8%). Dose adjustments

for hematologic toxicity are frequently needed. Neurotoxicity, manifested as paresthesis occurs in 10% of patients and may be severe in <1%. Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, edema and adult respiratory distress syndrome has been reported rarely following one or more doses of gemcitabine. Some patients experience the onset of pulmonary symptoms up to 2 weeks after the last dose. Other drug related adverse side effects are nausea/vomiting (9% of patients experience grade 3 or 4), diarrhea (3% of patients experience grade 3 or 4), transient elevations of one or both serum transaminases, fever (4% of patients experience grade 3 or 4), rash (1% of patients experience grade 3 or 4), flu-like symptoms, and alopecia (Van Cutsem et al 2004).

In premarketing studies conducted before the approval in Japan, 8 (1.8%) of 438 subjects died from a cause that may not be unrelated to gemcitabine. The causes of death consist of progression of cancer in 3 subjects, interstitial pneumonia in 2, sepsis in 2 and infective pneumonia in 1. The post-marketing safety data demonstrated that 1581 (74.9%) of 2110 non-small cell lung cancer patients experienced 4974 adverse side effects in total. In post-marketing studies, 238 (100%) of 238 subjects reported 4249 side effects in total. Major side effects reported include bone marrow depression, interstitial pneumonia, anaphylactoid symptoms, myocardial infarction, congestive cardiac failure, pulmonary oedema, bronchospasm, adult respiratory distress syndrome, renal failure, haemolytic uraemic syndrome, skin disorder, hepatic function disorder and jaundice. See also the package insert for an overview of the adverse events of single agent gemcitabine.

2.7 Benefit/risk and ethical assessment

As a novel, mechanism based, tumor sensitising agent, for use in combination with chemotherapy, AZD7762 could enhance the efficacy of any chemotherapy regimen which includes a DNA damaging agent for potential broad patient benefit.

AZD7762 should have an acceptable safety margin at the likely doses to be studied in this Phase I protocol. Further, there is no currently available evidence that suggests AZD7762 will affect the PK of gemcitabine.

In the first clinical study in Japanese using AZD7762, a conservative approach has been chosen to minimize patient risk. The starting dose is the same that in preceding overseas study (D1040C00002) and is much below that usually used in Phase I studies. Only patients with normal heart function will be eligible for the dose escalation phase and careful cardiac monitoring selected in discussion with an external cardiology consultant will be included.

Eligibility criteria in the dose-escalation phase exclude patients with cardiac ejection fractions less than 55%, New York Heart Association (NYHA) Status 2 to 4; second-degree heart block; a history of significant atherosclerotic cardiovascular disease in the past 6 months, prior administration of doxorubicin or other cardiotoxic anthracyclines, cardiac troponin T levels of CTCAE ≥grade 1 (see Section 7.3.5.1), and/or taking drugs with potent negative inotropic effect. Since decreases in contractility and blood pressure were seen in conscious telemetered dogs and were completely reversible within 4 h, blood pressure and pulse rate will be closely monitored for 4 hours after the start of the AZD7762 infusion. Echocardiograms (ECHO) will

be obtained within 2 to 6 hours after the start of the AZD7762 infusion (during Cycle 0 and 1, then prior to the start of each new cycle). In the event there is a decrease in ejection fraction by ≥10 points from baseline to a value <50 or an absolute decrease of ≥16% in an EF value that was above 50% for ≥24 hours, the ejection fraction will be measured again the following day to assess reversibility. If the EF is still ≥10 points from the baseline to a value < 50% or there is an absolute decrease of ≥16 % in an EF value that was above 50% this will be considered a DLT (see Section 4.1.6).

Troponin T is a sensitive, specific marker of cardiac damage and will be followed frequently. Pre-dose qualitative troponin T samples will be analysed, and dosing will not proceed (for Cycle 0, Cycle 1, and the first dose of all following cycles), until it has been confirmed that the patient does not have a positive (≥0.1 ng/mL) troponin T elevation. Participating center will identify a local cardiologist as much as possible who will be familiar with the pre-clinical safety data for AZD7762, and will participate in the study conduct and monitoring of patients.

Mild hematological and hepatic changes seen at low doses in the animal toxicology studies will be monitored in the clinic and, if they occur, are expected to be clinically manageable.

Provision is made in this study for dose omission or reduction if necessary based on type and severity/duration of AEs from recent treatment.

No reproductive toxicology or teratogenic studies have been conducted with AZD7762 to date, and it is unknown whether it is excreted in human milk. Since it will be administered in combination with gemcitabine, patients are advised that AZD7762 should not be administered to pregnant or breast-feeding women. However, women of child-bearing potential with cancer may enter clinical studies with AZD7762 provided they are fully informed of the lack of reproductive toxicity testing; have negative pregnancy test and use adequate contraception. In the event that pregnancy becomes to be known during the study, the subject should immediately be withdrawn from the study.

There is no known antidote to AZD7762. Investigators should be advised that any patient who inadvertently receives a higher dose than that specified in the study protocol should be managed with appropriate supportive care and be followed up expectantly.

Thus, the potential risk: benefit ratio for the FTIM Phase I studies appears acceptable in light of potential benefits, the initial patient eligibility criteria, proposed monitoring of patients, and safety margins.

3. STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this study is to assess safety and tolerability of AZD7762 alone and in combination with gemcitabine, by assessment of Common Terminology Criteria Adverse

Events version 3.0 (CTCAE) grade and type of adverse events (AEs), changes in laboratory values, vital signs, cardiac markers, ECG and left ventricular ejection fraction (LVEF).

3.2 Secondary objectives

The secondary objectives of the study are:

1. To determine the single-dose PK of AZD7762 when administered alone by assessment of Cmax, area under the plasma concentration-time curve from zero to infinity (AUC), area under the plasma concentration-time curve to the last quantifiable plasma concentration ($AUC_{(0-t)}$), clearance (CL), half-life associated with terminal slope of a semi-logarithmic concentration-time curve ($t_{½\lambda z}$), mean residence time (MRT), volume of distribution at steady state (V_{ss}), and plasma drug concentration at 24 hours after administration of a given dose (C_{24h})

2. To compare the clearance (CL) of AZD7762 and gemcitabine when given as a single agent to the corresponding CL value when AZD7762 and gemcitabine are given in combination

3. To seek preliminary evidence of the anti-tumor activity of AZD7762 administered in combination with gemcitabine by assessment of Response Evaluation Criteria in Solid Tumors (RECIST)

3.3 Exploratory objectives

The Exploratory objectives of the study are:

1. To explore the relationship between p53 and MDM2 tumor expression (and other genes/proteins implicated in the cell cycle) and clinical response

2. Optional: In consenting patients, to obtain a blood sample for DNA extraction for retrospective pharmacogenetic analysis

4. STUDY PLAN AND PROCEDURES

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

4.1 Overall study design and flow chart

This is an open-label, dose-escalation, Phase I study to evaluate the safety, tolerability, pharmacokinetics and tumor response of AZD7762 alone and in combination with gemcitabine.

Approximately 45 patients with advanced solid malignancies will be enrolled in this study, depending on the number of dose escalations required. A minimum of three and up to six evaluable patients will be enrolled in each dose level and in addition three evaluable patients

will be enrolled in the "PK espansion group". Investigators are encouraged to enroll patients with advanced solid malignancies for whom single-agent weekly gemcitabine therapy as described in this protocol is considered appropriate.

Regarding the combination therapy, following 2 schedules will be investigated in this study. This protocol procedures should be basically common for the Schedules A and B if not otherwise specified. Only Schedule B is specified when some of procedures are different between these Schedules.

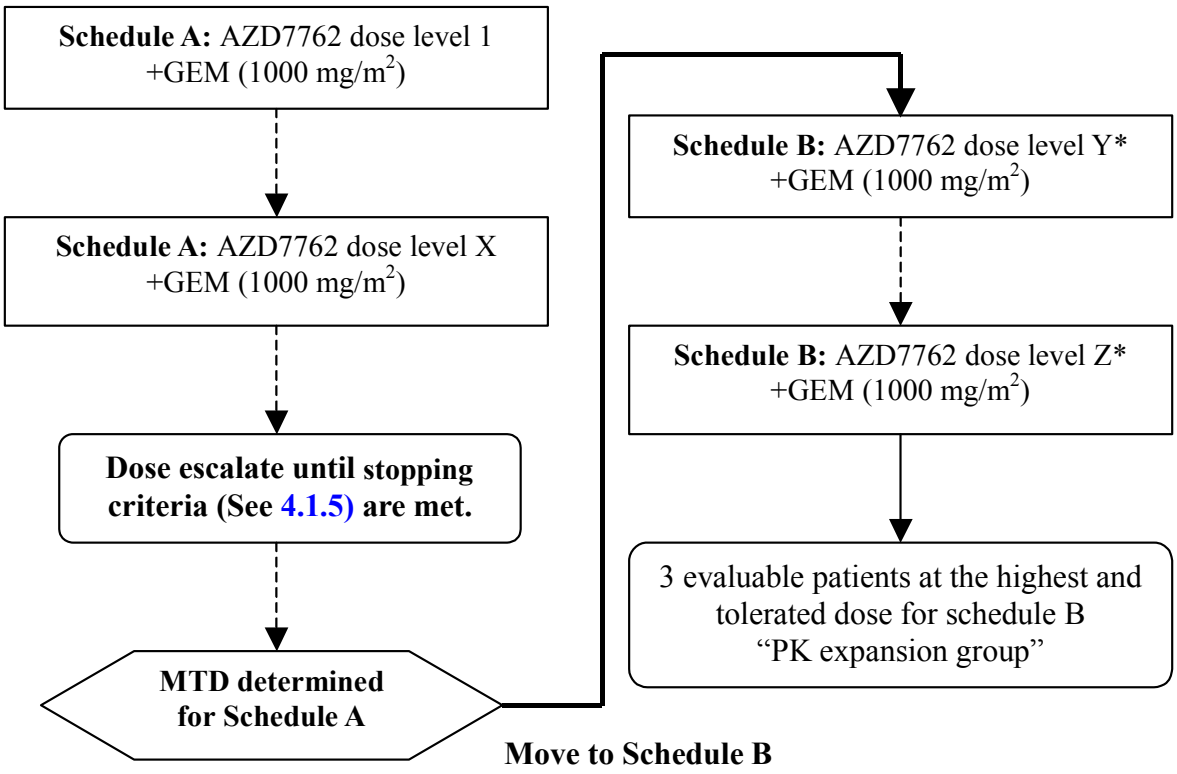
- Schedule A: AZD7762 in combination with gemcitabine once weekly for 2 weeks followed by a rest week

- Schedule B: AZD7762 in combination with gemcitabine once weekly for 3 weeks followed by a rest week*

* After completion of dose escalation will Schedule A, safety and tolerability of Schedule B will be evaluated at MTD and one lower dose level of that in Schedule A.

Once safety and tolerability of Schedule B is evaluated, three more patients will be incorporated into the cohort at the highest and tolerated dose in Schedule B to study the effect of AZD7762 on the PK of gemicitabine ("PK expansion group").

Figure 2 Study flow chart



*: After MTD is determined for Schedule A, tolerability of Schedule B will be evaluated at dose level Y (one lower level of MTD for Schedule A) and dose level Z (same level as MTD for Schedule A). If the dose level Y is not tolerated, then tolerability will be evaluated at one lower level of that dose.

4.1.1 Treatment schedule

Cycle 0: Patients will receive a single dose of AZD7762, administered as a 60-minute IV infusion on Days 1 and 8. Each patient will be observed for safety until Day 15 when Cycle 1 begins. PK profile blood samples will be collected following the first single agent dose of AZD7762 in Cycle 0.

Cycle 0 will be omitted for the patients in Schedule B and the "PK expansion group". For the patients, the first administration will be on Cycle 1, Day 1.

Cycle 1: Patients will receive combination treatment with gemcitabine and AZD7762 (providing dose-limiting toxicity (DLT) (defined in Section 4.1.6) is not encountered in Cycle 0). The same dose of AZD7762 will be used for Cycle 0 and Cycle 1 in each patient. Gemcitabine will be administered as a 30-minute IV infusion. AZD7762 will be administered as a 60-minute IV infusion. AZD7762 infusion will start immediately upon completion of the gemcitabine infusion from Cycle 1 onwards. Treatment will be administered weekly for a total of 2 doses (or 3 doses in Schedule B and the "PK expansion group"). Each patient will then complete a safety evaluation. If second or third doses are omitted for tolerability reasons,

a maximum of one and within a week "make up dose" is permitted. PK profile blood samples will be collected following the second combination dose (on day 8 or at "make up dose" if a dose is omitted on day 8).

For the patients in the "PK expansion group", only gemcitabine will be administered on Cycle 1, Day 1, AZD7762 will be administered from Cycle 1, Day 8.

Cycle 2 onwards: Following the completion of Cycles 0 and 1, individual patients may continue treatment indefinitely after giving consent to the continued study treatment, provided that in the opinion of the Investigator: (a) they are continuing to benefit, (b) there is no evidence of disease progression, and (c) they do not meet any other withdrawal criteria (see Section 5.5).

AZD7762 will be administered immediately after the gemcitabine infusion. The dose of AZD7762 administered in Cycle 2 onwards will normally be the same as in Cycles 0 and 1, however see Section 6.4.4.3 and Section 6.4.4.4 for permitted intra-patient dose changes of gemcitabine and AZD7762 respectively

4.1.2 Dose-escalation decision

Prior to each dose escalation, the Investigators and AstraZeneca will review the required safety and tolerability data from all patients treated during Cycle 0 and Cycle 1, and the PK data from Cycle 0 (and from the prior cohort for Cycle 1 if available).

AZD7762 dose escalation (whether to escalate the dose in the next patient cohort, and by how much), will occur based on the required safety, tolerability, and PK information obtained from a minimum of 3 evaluable patients, during Cycles 0 and 1 of treatment.

For dose-escalation decisions, an evaluable patient is defined as a patient who:

- Experienced DLT within Cycle 0 or Cycle 1,

  Or

- Completed Cycle 0 and Cycle 1 of treatment

  – As a result of dose adjustment regulated in Section 6.4.4.3 and Section 6.4.4.4, patients with 75% or higher ratio of the actual dose to the planned dose in a cycle (those with less than 75% will be considered as non-evaluable patients and new subjects will be included for the replacement)

  – Regarding dose omission, patients with a maximum of one dose omission by 1 week or less, following the Section 4.1.1, will be considered as evaluable patients (those who required dose omission exceeding the above duration will be considered as non-evaluable patients, and new subjects will be included for the replacement.)

NB. If a patient progresses after receiving 2 (or 3 in Schedule B) combination doses of gemcitabine and AZD7762 in Cycle 1 (ie, during the last rest week), the patient may still be evaluable for dose escalation decisions (ie, there is no need to replace that patient).

After review of data from ≥3 evaluable patients in a cohort, the following criteria will be used to determine the need for dose escalation; (1) severity of any observed drug-related toxicity during Cycles 0 and 1 of treatment, and (2) the estimated PK parameter data for AZD7762 obtained in Cycle 0 of treatment (and Cycle 1 if available)

In all cases, one of the following actions will be recommended:

- Proceed with dose level –1 (applies only to the starting dose cohort)
- No DLT: Proceed with dose escalation
- 1 DLT: Expand the cohort to up to 6 evaluable patients if less than 6 patients evaluated at that dose level
- De-escalate the dose: either to a previous lower dose level (in such cases cohorts may be expanded up to 6 evaluable patients at each dose level), or to a new lower intermediate dose level
- Terminate the study

4.1.3 Criteria for dose escalation

The starting dose of AZD7762 will be 6 mg administered IV over 60 minutes.

Prior to each dose escalation, the Dose Escalation Committee (the members consist of the Study Delivery Team Physician, other members in AstraZeneca K.K. and the principal investigator) will select a dose of AZD7762 in the next patient cohort based on the available safety and PK data from all evaluable patients treated during Cycle 0 and Cycle1 and from the cohorts confirmed safety in the study D1040C00002. The dose Escalation Committee should be discussed with the Data and Safety Monitoring Committee as needed to make a final decision.

The dose of AZD7762 will be escalated until <u>any one</u> of the following criteria are met. Otherwise, subsequent doses will proceed by ≤50% dose increments until any of the other stopping criteria in Section 4.1.5 are met.

1. A patient experiences a ≥CTCAE grade 2 toxicity in Cycle 0 (except troponin T)
2. A patient experiences a protocol defined DLT in Cycle 0 to 1
3. The **mean** C_{24h} of AZD7762 in a cohort is ≥100 ng/mL

It is estimated that in man a dose of 160 mg/m^2 or 270 mg will result in a C_{24h} of ≥100 ng/mL. A 160-mg/m^2 dose in conscious dog produced a mild cardiac contractility change at C_{max}. 100 ng/mL is also twenty-eight times the EC_{50} for Chk1 and should assure adequate Chk1 inhibition.

Intermediate doses between those currently listed in the protocol may be selected by the Dose Escalation Committee based on emerging safety and/or PK data, including: non-linear PK, difficult to interpret events resulting from the combination treatment, AEs not predicted from the pre-clinical data, etc.

4.1.4 Criteria for dose escalation cohort size

The following rules will apply for dose escalation cohort size (illustrated in Figure 3):

- If no DLTs occur in a cohort of ≥3 evaluable patients, and the PK criterion for stopping dose escalation has not been met (Section 4.1.5, criterion 3), dose escalation in a new cohort of ≥3 evaluable patients will occur.
  - If no DLTs occur in a cohort of ≥3 patients, but the PK criterion for stopping dose escalation is met, then that cohort may be expanded to 6 evaluable patients.
- If a grade 1 quantitative troponin T elevation (see Section 7.3.5.1) occurs at any 2 time points in cycles 0 or 1 or any ≥ Grade 2 quantitative troponin T elevation occurs in cycle 0 or 1, in the absence of concurrent explanatory event (eg, sepsis, pulmonary embolism [PE]), that dose will be considered as non-tolerated, dose escalation will stop and the previous cohort will be expanded to 6 evaluable patients if not already (a new intermediate lower dose may also be considered).
- If any other protocol-defined DLT is observed in 1 out of ≥3 evaluable patients, that cohort will be expanded up to a maximum of 6 evaluable patients.
  - If no more than 1 patient in the expanded cohort experiences a protocol-defined DLT (other than troponin T elevation, as above), then the dose will be considered tolerable and dose-escalation may recommence, again providing that the PK criterion for stopping dose escalation has not been met (Section 4.1.5, criterion 3).
- If any protocol-defined DLT is observed in 2 or more patients in any cohort, this dose will be considered as non-tolerated and dose-escalation will stop. The previous cohort will then be expanded to 6 evaluable patients if not already (a new intermediate lower dose may also be considered). The amount of dose escalation will be determined using the criteria in Section 4.1.3.

4.1.5 Stopping criteria for dose-escalation

Dose escalation will stop based on any of the following toxicity or PK criteria:

1. If a grade 1 quantitative troponin T elevation (see Section 7.3.5.1) occurs at any 2 time points in cycles 0 or 1 or any ≥ Grade 2 quantitative troponin T elevation occurs in cycle 0 or 1, in the absence of concurrent explanatory event (eg, sepsis, PE)

2. If any other DLT is observed in 2 or more patients

3. If the C_{24h} of AZD7762 is ≥100 ng/mL for **all** patients in the cohort

Criteria for dose escalation are also illustrated in Figure 3.

In addition to the above, if any grade 4 quantitative troponin T elevation, in absence of a well defined concurrent event such as sepsis or PE, is seen in any patient at a dose level in any cycle, all patients at that dose level will cease AZD7762 treatment and no further patients will be enrolled at that dose level. Consultation from expert cardiologists will be obtained.

4.1.6 Definitions of dose-limiting toxicity (DLT)

An event will be defined as a DLT if it is drug-related and meets one of the following criteria, and it occurs within Cycle 0 or 1. Events or lab abnormalities clearly due to disease progression will not be considered a DLT. The Dose Escalation Committee will determine DLTs.

Cycle 0 – single agent AZD7762:

- CTCAE grade 1 quantitative troponin T elevation (see Section 7.3.5.1), at a minimum of two separate time points in cycle 0, in absence of a well defined concurrent event such as sepsis or PE
- Any CTCAE ≥ grade 2 quantitative troponin T elevation (see Section 7.3.5.1) in absence of a well-defined concurrent event, such as sepsis or PE
- CTCAE ≥grade 2 ejection fraction with a value representing a minimum 10 point decrease from baseline to a value < 50% or an absolute decrease of ≥16% in an EF value that was above 50% for ≥ 24 h post dose
- CTCAE ≥ grade 3 toxicity
- CTCAE ≥ grade 2 cardiac toxicity (except troponin T) lasting greater than 24 hours
- In the view of Astrazeneca and the Investigators any other unacceptable toxicity profiles are encountered

Cycle 1 – gemcitabine/AZD7762 combination:

- CTCAE grade 1 quantitative troponin T elevation (see Section 7.3.5.1) at a minimum of two separate time points in cycle 1 or across cycles 0 and 1, in absence of a well defined concurrent event such as sepsis or PE
- Any CTCAE ≥ grade 2 quantitative troponin T elevation (see Section 7.3.5.1) in absence of a well-defined concurrent event, such as sepsis or PE
- CTCAE ≥grade 2 ejection fraction with a value representing a minimum 10 point decrease from baseline to a value <50% or an absolute decrease of ≥16% in an EF value that was above 50% for ≥24 h post dose
- CTCAE ≥ grade 4 neutropenia for more than 4 days, or CTCAE ≥ grade 3 neutropenia complicated ≥38.5° C fever (≥38.0°C if axillary)
- CTCAE ≥ grade 3 ALT and/or AST elevation in patients with liver metastases lasting >7 days
- CTCAE ≥ grade 3 nausea or emesis for more than 24 hours despite aggressive management
- CTCAE ≥ grade 3 diarrhea for more than 24 hours despite aggressive management
- CTCAE ≥ grade 4 haematologic toxicity (see above for neutropenia)
- CTCAE ≥ grade 3 non-hematological toxicity
- CTCAE ≥ grade 3 Lab abnormalities at two consecutive timepoints within 2 days
- In the view of Astrazeneca and the Investigators any other unacceptable toxicity profiles encountered

Individual patients who experience a DLT (other than troponin T elevation, see below) may continue to receive study treatment upon recovery.

Individual patients who experience a troponin T elevation, that meets the definition of a DLT, in absence of a well defined concurrent event such as sepsis or PE should be withdrawn from treatment and followed up accordingly. All patients who experience a troponin T elevation are required to have CPK measurements and ECG as well as Echocardiogram and any additional follow –up deemed necessary by the investigator.

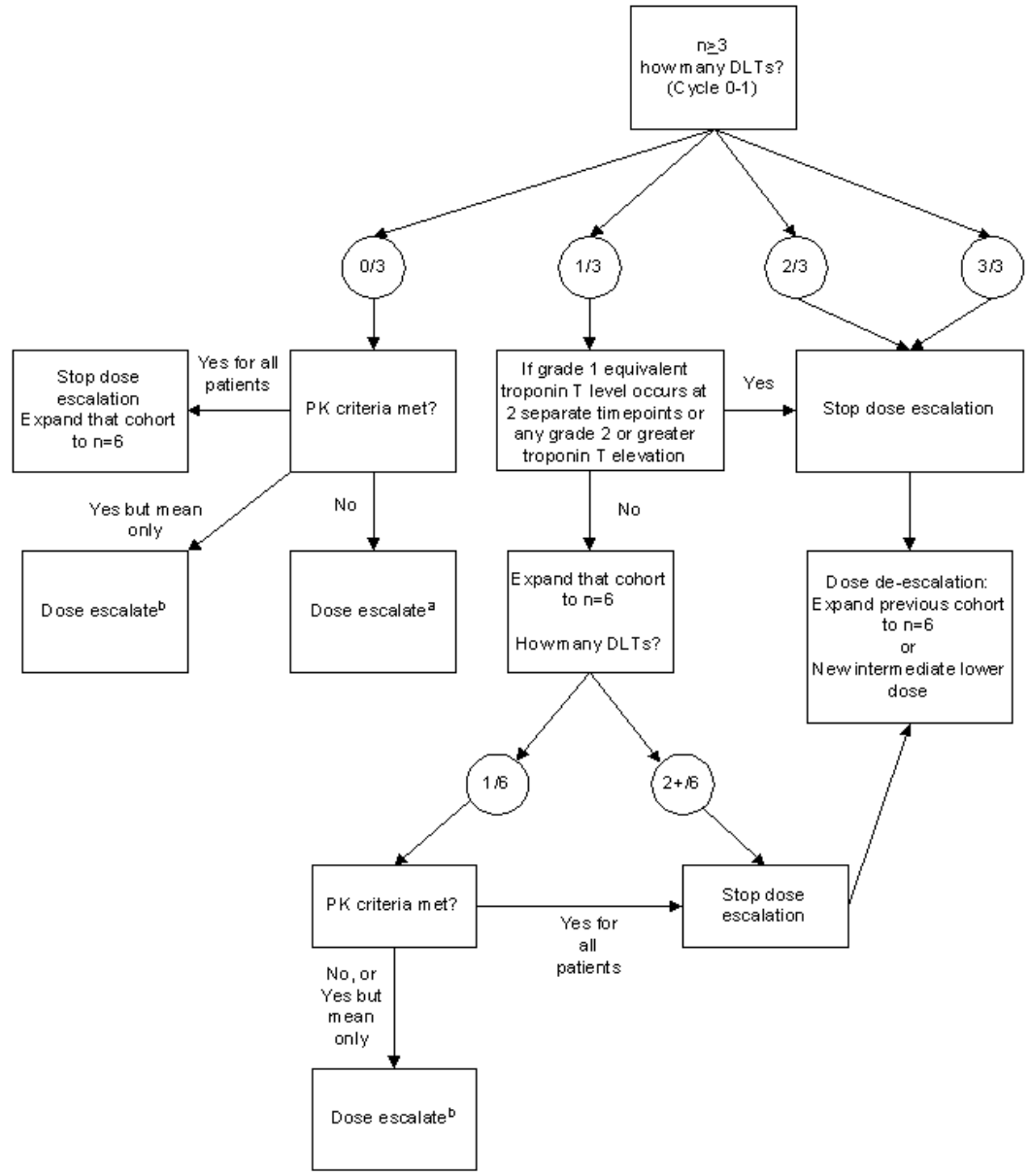
Study treatment should be held in patients who experience a DLT or intolerable AE. Patients who continue to benefit from therapy and recover from the DLT (or intolerable AE) to ≤CTCAE grade 2 or baseline within 4 weeks may resume the study medication at a lower dose level after discussion and agreement with AstraZeneca and giving consent to the study continuation. In that case, Cycle 1 should be regarded as having completed and the patient

will resume the treatment from Cycle 2. Patients who fail to recover or have a recurrent DLT or intolerable AE will be withdrawn from the study treatment and be followed for 30 days after the last administration of AZD7762.

4.1.7 Definition of maximum-tolerated dose (MTD)

In this study, the MTD of AZD7762 will be defined as the highest, safely tolerated dose, within Cycles 0 and 1, that causes reversible toxicity, and does not subject patients to excessive risk or discomfort, and will ordinarily be considered the dose level immediately below the level where definitive toxicity occurs (a minimum of two patients with DLTs).

Figure 3 Dose-escalation decision tree



a Dose escalation by a maximum of 50% or less if previous dose escalations have been 50%, or if a patient has experienced Grade 2 toxicity or higher in Cycle 0

b Dose escalation by a maximum 50%
intermediate dose escalation (eg, 25%) may also take place depending on the emerging toxicity and PK profile

Table 1 Study Plan: Schedule A

	Screen	**Cycle 0**		**Cycle 1**			**Cycle 2**			**Cycle 3+**				Safety follow-up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**	**11+**	**12+**	**99**	
Visit Description	**Screen**	Week 1 Day 1	Week 2 Day 8	Week 1 Day 1	Week 2 Day 8	Week 3 Day 15	Week 1 Day 1	Week 2 Day 8	Week 3 Day 15	Week 1 Day 1	Week 2 Day 8	Week 3 Day 15	Comp-letion	≥30 days after the final dosing
Visit Window (n wks ± n d)	0-4 w before Visit 2	0-4 w after Visit 1	1 w (±3d) after Visit 2	1 w (-3/ +10d) after Visit 3	1 w (-1/+2d) after Visit 4	1 w (-1/+2d) after Visit 5	1 w (±3d) after Visit 6	1 w (-1/+2d) after Visit 7	1 w (-1/+2d) after Visit 8	1 w (±3d) after previous Visit	1 w (-1/+2d) after previous Visit	1 w (-1/+2d) after previous Visit		
Informed consent[a]	X						X							
Past Medical history	X													
Eligibility criteria	X													
Physical examination	X													
Pregnancy test (pre-menopausal females only)	X												X	
WHO PS	X													
Administer AZD7762		X	X	X	X		X	X		X	X			
Administer gemcitabine				X	X		X	X		X	X			
Vitals signs[b]	X	X[b]	X	X[b]	X	X	X			X			X	
Hematology[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clin chem[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X		X			X			X			X q 3 cycles	X	

Table 1 Study Plan: Schedule A

	Screen	**Cycle 0**		**Cycle 1**			**Cycle 2**			**Cycle 3+**				Safety follow-up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**	**11+**	**12+**	**99**	
Visit Description	**Screen**	Week 1 Day 1	Week 2 Day 8	Week 1 Day 1	Week 2 Day 8	Week 3 Day 15	Week 1 Day 1	Week 2 Day 8	Week 3 Day 15	Week 1 Day 1	Week 2 Day 8	Week 3 Day 15	Comp-letion	≥30 days after the final dosing
Visit Window (n wks ± n d)	0-4 w before Visit 2	0-4 w after Visit 1	1 w (±3d) after Visit 2	1 w (-3/ +10d) after Visit 3	1 w (-1/+2d) after Visit 4	1 w (-1/+2d) after Visit 5	1 w (±3d) after Visit 6	1 w (-1/+2d) after Visit 7	1 w (-1/+2d) after Visit 8	1 w (±3d) after previous Visit	1 w (-1/+2d) after previous Visit	1 w (-1/+2d) after previous Visit		
Troponin T (quantitative & qualitative) [d]	X	X[d]	X[d]	X[d]	X[d]		X[d]			X[d]			X	
CPK [e]	X			X (pre)			X (pre)			X (pre)			X	
BNP [f]	X													
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Conc Meds [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECHO & ECG [h]	X	X	X	X	X		X		X	X		X		
Chest X-ray [i]	X					X			X			X		
Tumor evaluation (RECIST) [j]	X[a]		X (Day 10-15) [j]							X q 3 cycles			X	
PK blood for AZD7762 [k]		X	X	X	X[l]									
Archived tumor [m]	X													
Blood for germline genetics [n]	X													

a Written informed consent must be obtained prior to any study specific assessments. If written approval is obtained from the patient, only tumor assessment data obtained before informed consent may be used if there are available data obtained within 4 weeks before the first administration.. To

continue treatment in Cycle 2 onwards, informed consent for the continued study treatment should be obtained from the patient before start of Cycle 2 (The same procedure should also be applied when a patient who develops DLT or intolerable adverse event and held the treatment during Cycle 1 resumes the study treatment. See Section 4.1.6).

b Blood pressure (BP), heart rate (HR) and body temperature (BT) to be taken at screening and routinely with each visit through Cycle 1, then at the beginning of each cycle. Cycle 0, Day 1 BP and HR to be taken prior to AZD7762, and at 0.5, 1, 1.5, 2, 3, and 4 h after the start of AZD7762 infusion (BT to be taken only prior to AZD7762 infusion). Cycle 1, Day 1 BP and HR to be taken prior to gemcitabine infusion, and then prior to AZD7762 infusion, and at 0.5, 1, 1.5, 2, 3, and 4 h after the start of AZD7762 infusion (BT to be taken only prior to gemcitabine infusion). Height and weight obtained at screening. Weight obtained on Cycle 0, Day 1 then per clinic routine (If screen data of weight is obtained within 3 days prior to Cycle 0, Day 1. the screen data may be used as the data for Visit 2.)

c Hematology and chemistry labs to be obtained up to 3 days prior to Cycle 0, Day 1 (Visit 2). If screen data are obtained within 3 days prior to Cycle 0, Day 1, the screen data may be used as the data for Visit 2. After Cycle 0, Day 1, hematology and chemistry labs to be obtained up to 1 day prior to the study dosing. See Section 7.3.5 for the specific labs to be drawn. If neutropenia is seen, obtain hematology labs twice a week if deemed medically necessary by the investigator.

d Cardiac troponin T quantitative measurements at: (a) screening, (b) at baseline, 4, 8, 24, 48 and 72 h after single dose 1 (Cycle 0, Day 1), (c) pre-dose, then 4 and 24 h after single dose 2 (Cycle 0, Day 8), (d) pre-dose, then 4, 24, 48, 72 h after the start of AZD7762 infusion (Cycle 1, Day 1), (e) pre-dose, then 4 h after the start of AZD7762 infusion (Cycle 1, Day 8), (f) pre-dose, then 4 h after the start of AZD7762 infusion (Cycle 2, Day 1), and (g) thereafter following the first dose (pre-dose and 4 h post-dose) of each cycle. Subsequent levels as indicated clinically, or if an intra-patient dose escalation of AZD7762 occurs. If screen data is obtained within 3 days prior to Cycle 0, Day 1. the screen data may be used as the data for Visit 2. Pre-dose qualitative troponin T will also be measured, and dosing will not proceed (for Cycles 0-1, and the first dose of all following cycles), until it has been confirmed that the patient does not have a positive (≥0.1 ng/mL) elevation. Timings are based on the start of the AZD7762 infusion. See Section 7.3.5.1 for Troponin T sample time windows

e Creatine phosphokinase (CPK) measurements at: (a) screening, (b) pre-dose on Cycle 1, Day 1, (c) thereafter pre-dose on Day 1 of each Cycle and (d) required in the event of an elevated troponin T level. Subsequent levels as indicated clinically.

f Natriuretic brain peptide (BNP) at screening and to be repeated only if symptoms of congestive heart failure or shortness of breath occur

g Concomitant medications to be collected from the time they sign the consent form and then assessed at each visit to record any change.

h Echocardiogram (ECHO) and electrocardiogram (ECG) will be performed (a) pre-study, (b) Cycle 0, Day 1 (c) Cycle 0, Day 8 (d) Cycle 1, Day 1, (e) Cycle 1, Day 8, (f) Cycle 2, Day 1, (g) and then routinely following the first dose and on the last week (rest) of each cycle (up to 7 days prior to the first dose of each Cycle – pre-dose on the first day of each Cycle is permitted instead of the previous rest week if preferred). For dosing days the assessments will be performed between 2-6 h after the start of the AZD7762 infusion. If EF declines by ≥10 points from baseline to a value <50% or there is an absolute decrease of ≥16 % in an EF value that was above 50% for ≥ 24 hour, follow up must be repeated the following day. An ECG is also required in the event of an elevated local or central troponin T level.

i Chest X-ray will be performed at screening and on the last week (rest) of each cycle (up to 7 days prior to the first dose of each Cycle – pre-dose on the first day of each Cycle is permitted instead of the previous rest week if preferred). If chest CT scan is performed as a part of tumor evaluations during the time window of chest X-ray, chest X-ray is not mandatory.

j Tumor Evaluations (RECIST) assessments to be performed at baseline, Cycle 0 (between Day 10 and 15) only if not previously obtained within 28 days of first combination dose of AZD7762 and Gemcitabine (Cycle1, Day 1), Cycle 3, Day 1 (within 7 days prior to gemcitabine) and then every 3 cycle (±2 weeks). Patients who have been withdrawn from study therapy prior to disease progression should, where possible, have a post study assessment approximately 4 weeks from date of last dose. Patients who have a response should have repeat scan 4-6 weeks later to confirm response

k See Appendix E for the specific PK schedule for AZD7762 and gemcitabine

l If the situation arises whereby the dose on Cycle 1, Day 8 is omitted for tolerability reasons, PK blood samples will be collected following the next administered combination dose

m Paraffin embedded tumor tissue obtained at time of diagnosis or other time before this clinical study will be collected (sample does not have to be provided to AstraZeneca prior to commencement of study related treatment)

n Provision of this sample is optional and includes only consenting patients

Table 2 Summary of Patient visits: screen to Cycle 1: Schedule A

Visit	Summary of main activities
Screen	Pregnancy test (pre-menopausal females only), vital sign, height, weight, thematology, chemistry, urinalysis, quantitative troponin T, CPK, BNP, ECHO/ECG, chest CX-ray[a], RECIST, germline genetics (optional) (refer to Section 7.2 for full details)
Cycle 0, Day 1	Vital sign, weight, hematology, chemistry, **Single agent AZD7762 dose 1**, quantitative troponin T (pre-dose [incl. qual], 4 h, 8 h), ECHO/ECG (2-6 h after the start of the AZD7762 infusion), PK
Cycle 0, Day 2	Quantitative troponin T (24 h), PK
Cycle 0, Day 3	Quantitative troponin T (48 h), PK
Cycle 0, Day 4	Quantitative troponin T (72 h)
Cycle 0, Day 8	Vital sign, hematology, chemistry, urinalysis, PK, **Single agent AZD7762 dose 2**, quantitative troponin T (pre-dose [incl. qual], 4 h), ECHO/ECG (2-6 h after the start of the AZD7762 infusion)
Cycle 0, Day 9	Quantitative troponin T (24 h)
Cycle 0, Day 10-15	RECIST (only if not performed within 28 days of first combination dose)
Cycle 1, Day 1	Vital sign, hematology, chemistry, **Combination dose 1**, quantitative troponin T (pre-dose [incl. qual], 4 h), CPK, ECHO/ECG (2-6 h after the start of the AZD7762 infusion), PK
Cycle 1, Day 2	Quantitative troponin T (24 h), PK
Cycle 1, Day 3	Quantitative troponin T (48 h)
Cycle 1, Day 4	Quantitative troponin T (72 h)
Cycle 1, Day 8	Vital sign, hematology, chemistry , **Combination dose 2**, quantitative troponin T (pre-dose [incl. qual], 4 h), ECHO/ECG (2-6 h after the start of the AZD7762 infusion), PK
Cycle 1, Day 9	PK
Cycle 1, Day 10	PK
Cycle 1, Day 15	Vital sign, hematology, chemistry, urinalysis, chest X-ray (until pre-dose on Cycle 2, Day 1[a]), Rest

a If chest CT scan is performed as a part of tumor evaluations during the time window of chest X-ray, chest X-ray is not mandatory.

Table 3 Study Plan: Schedule B and the PK expansion group

	Cycle 1				**Cycle 2**				**Cycle 3+**			
Visit [a, b]	**4**	**5**	**5.5**	**6**	**7**	**8**	**8.5**	**9**	**10+**	**11+**	**11.5+**	**12+**
Visit Description[b]	Week 1 Day 1	Week 2 Day 8	Week 3 Day 15	Week 4 Day 22	Week 1 Day 1	Week 2 Day 8	Week 3 Day 15	Week 4 Day 22	Week 1 Day 1	Week 2 Day 8	Week 3 Day 15	Week 4 Day 22
Visit Window (n wks ± n d)	0-4 w after Visit 1[b]	1 w (-1/+2d) after Visit 4	1 w (-1/+2d) after Visit 5	1 w (-1/+2d) after Visit 5.5	1 w (±3d) after Visit 6	1 w (-1/+2d) after Visit 7	1 w (-1/+2d) after Visit 8	1 w (-1/+2d) after Visit 8.5	1 w (±3d) after previous Visit	1 w (-1/+2d) after previous Visit	1 w (-1/+2d) after previous Visit	1 w (-1/+2d) after previous Visit
Informed consent[c]					X							
Administer AZD7762[d]	X[d]	X	X		X	X	X		X	X	X	
Administer gemcitabine[d]	X[d]	X	X		X	X	X		X	X	X	
Vitals signs[e]	X[e]	X	X	X	X				X			
Hematology[f]	X	X	X	X	X	X	X	X	X	X	X	X
Clin chem[f]	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis				X				X				X q 3 cycles
Troponin T (quantitative & qualitative)[g]	X[g]	X[g]	X[g]		X[g]				X[g]			
CPK[h]	X (pre)				X (pre)				X (pre)			
ECHO & ECG[i]	X	X	X		X			X	X			X
Chest X-ray[j]				X				X				X
Tumor evaluation (RECIST)[k]									X q 2 cycles			
PK blood for AZD7762[l]		X[m]										

	Cycle 1				Cycle 2				Cycle 3+			
Visit [a, b]	**4**	**5**	**5.5**	**6**	**7**	**8**	**8.5**	**9**	**10+**	**11+**	**11.5+**	**12+**
Visit Description[b]	Week 1 Day 1	Week 2 Day 8	Week 3 Day 15	Week 4 Day 22	Week 1 Day 1	Week 2 Day 8	Week 3 Day 15	Week 4 Day 22	Week 1 Day 1	Week 2 Day 8	Week 3 Day 15	Week 4 Day 22
Visit Window (n wks ± n d)	0-4 w after Visit 1[b]	1 w (-1/+2d) after Visit 4	1 w (-1/+2d) after Visit 5	1 w (-1/+2d) after Visit 5.5	1 w (±3d) after Visit 6	1 w (-1/+2d) after Visit 7	1 w (-1/+2d) after Visit 8	1 w (-1/+2d) after Visit 8.5	1 w (±3d) after previous Visit	1 w (-1/+2d) after previous Visit	1 w (-1/+2d) after previous Visit	1 w (-1/+2d) after previous Visit
PK blood for gemcitabine[l]	X	X[m]										

a See Table 1 for schedule at screen, completion and safety follow-up. Adverse events and concomitant medications are to be collected at every visit throughout the study.

b Cycle 0 will be omitted for patients in Schedule B ant the "PK expansion group". For the patients, the first administration will be on Cycle 1, Day 1. Visit 4 will follow Visit 1 and the window for Visit 4 is the same as Visit 2.

c To continue treatment in Cycle 2 onwards, informed consent for the continued study treatment should be obtained from the patient before start of Cycle 2 (The same procedure should also be applied when a patient who develops DLT or intolerable adverse event and held the treatment during Cycle 1 resumes the study treatment. See Section 4.1.6).

d For the patients in the "PK expansion group", only gemcitabine will be administered on Cycle 1, Day 1, AZD7762 will be administered from Cycle 1, Day 8.

e Blood pressure (BP), heart rate (HR) and body temperature (BT) to be taken routinely with each visit through Cycle 1, then at the beginning of each cycle. Cycle 1, Day 1 BP and HR to be taken prior to gemcitabine infusion, and then prior to AZD7762 infusion, and at 0.5, 1, 1.5, 2, 3, and 4 h after the start of AZD7762 infusion (BT to be taken only prior to gemcitabine infusion).

f Hematology and chemistry labs to be obtained up to 1 day prior to the study dosing. See Section 7.3.5 for the specific labs to be drawn. If neutropenia is seen, obtain hematology labs twice a week if deemed medically necessary by the investigator.

g Cardiac troponin T quantitative measurements at: (a) pre-dose, then 4, 24, 48, 72 h after the start of AZD7762 infusion (Cycle 1, Day 1), (b) pre-dose, then 4 h after the start of AZD7762 infusion (Cycle 1, Day 8), (c) pre-dose, then 4 h after the start of AZD7762 infusion (Cycle 1, Day 15), (d) pre-dose, then 4 h after the start of AZD7762 infusion (Cycle 2, Day 1), and (e) thereafter following the first dose (pre-dose and 4 h post-dose) of each cycle. Subsequent levels as indicated clinically, or if an intra-patient dose escalation of AZD7762 occurs. Pre-dose qualitative troponin T will also be measured, and dosing will not proceed (for Cycle 1, and the first dose of all following cycles), until it has been confirmed that the patient does not have a positive (≥0.1 ng/mL) elevation. Timings are based on the start of the AZD7762 infusion. See Section 7.3.5.1 for troponin T sample time windows

h Creatine phosphokinase (CPK) to be measurementd at pre-dose on Cycle 1, Day 1, thereafter pre-dose on Day 1 of each Cycle and required in the event of an elevated troponin T level. Subsequent levels as indicated clinically.

i Echocardiogram (ECHO) and electrocardiogram (ECG) will be performed on (a) Cycle 1, Day 1, (b) Cycle 1, Day 8, (c) Cycle 1, Day 15, (d) Cycle 2, Day 1, (e) and then routinely following the first dose and on the last week (rest) of each cycle (up to 7 days prior to the first dose of each Cycle – pre-dose on the first day of each Cycle is permitted instead of the previous rest week if preferred). For dosing days the assessments will be performed

between 2-6 h after the start of the AZD7762 infusion. If EF declines by ≥10 points from baseline to a value <50% or there is an absolute decrease of ≥16 % in an EF value that was above 50% for ≥ 24 hour, follow up must be repeated the following day. An ECG is also required in the event of an elevated local or central troponin T level.

j Chest X-ray will be performed at screening and on the last week (rest) of each cycle (up to 7 days prior to the first dose of each Cycle – pre-dose on the first day of each Cycle is permitted instead of the previous rest week if preferred). If chest CT scan is performed as a part of tumor evaluations during the time window of chest X-ray, chest X- ray is not mandatory.

k Tumor Evaluations (RECIST) assessments to be performed at Cycle 3, Day 1 (within 7 days prior to gemcitabine) and then every 2 cycle (±2 weeks). Patients who have been withdrawn from study therapy prior to disease progression should, where possible, have a post study assessment approximately 4 weeks from date of last dose. Patients who have a response should have repeat scan 4-6 weeks later to confirm response

l PK blood for AZD7762 and gemcitabine will be sampled only from the patients in the "PK expansion group". See Appendix E for the specific PK schedule for AZD7762 and gemcitabine

m If the situation arises whereby the dose on Cycle 1, Day 8 is omitted for tolerability reasons, PK blood samples will be collected following the next administered combination dose

Table 4 Summary of Patient visits: screen to Cycle 1: Schedule B and "PK expansion group"

Visit [a]	Summary of main activities
screen	Refer to Table 2 and Section 7.2
Cycle 1, Day 1	Vital sign, hematology, chemistry, **Combination dose 1**, quantitative troponin T (pre-dose [incl. qual], 4 h), CPK, ECHO/ECG (2-6 h after the start of the AZD7762 infusion), PK [b]
Cycle 1, Day 2	Quantitative troponin T (24 h)
Cycle 1, Day 3	Quantitative troponin T (48 h)
Cycle 1, Day 4	Quantitative troponin T (72 h)
Cycle 1, Day 8	Vital sign, hematology, chemistry , **Combination dose 2**, quantitative troponin T (pre-dose [incl. qual], 4 h), ECHO/ECG (2-6 h after the start of the AZD7762 infusion), PK [b]
Cycle 1, Day 9	PK [b]
Cycle 1, Day 10	PK [b]
Cycle 1, Day 15	Vital sign, hematology, chemistry , **Combination dose 3**, quantitative troponin T (pre-dose [incl. qual], 4 h), ECHO/ECG (2-6 h after the start of the AZD7762 infusion)
Cycle 1, Day 22	Vital sign, hematology, chemistry, urinalysis, chest X-ray (until pre-dose on Cycle 2, Day 1[c]), Rest

a Cycle 0 will be omitted for patients in Schedule B and the "PK expansion group".
b PK sampling is applicable for the patients in the "PK expansion group" only.
c If chest CT scan is performed as a part of tumor evaluations during the time window of chest X-ray, chest X-ray is not mandatory.

4.2 Rationale for study design, doses and control groups

4.2.1 Rationale for study design and doses

This is an open-label, dose escalation, Phase I study to evaluate the safety, tolerability, PK and tumor response of AZD7762 alone and in combination with gemcitabine. The number of patients is therefore based on the desire to gain adequate information while exposing as few patients as possible to the study medication and procedures.

Since all adverse events were evident in pre-clinical toxicology in the first week, AZD7762 will be administered as a single agent on two consecutive weeks with safety observation period completed on Day 15 for each patient in the dose-escalation phase. This will allow evaluation of safety and PK for single agent prior to evaluation of safety and PK for the combination.

Dose escalations will be decided by the Dose Escalation Committee based on emerging safety and/or PK data during this study, and dose escalation will proceed until predefined safety or PK limits or MTD defined in preceding study D1040C00002 are reached.

In the ongoing overseas study D1040C00002, the subjects, similar to those in this study, will receive the combination therapy with escalating doses of AZD7762 and gemcitabine according to Schedule A during the dose escalation phase, ie, the treatment is given once weekly for 2 consecutive weeks followed by a one week washout. The dose escalation will proceed until DLTs occur (more than 1 subject) or any pharmacokinetically-defined escalation stopping criterion is met. This study will start with the schedule A. After the end of the dose escalation, the safety, tolerability and pharmacokinetics of AZD7762 will be assessed under Schedule B, ie, the MTD identified in Schedule A and one level lower dose than the MTD will be given in combination with gemcitabine for three consecutive weeks followed by a one week washout. To avoid possible risks to the patients associated with the schedule change from A to B, the one level lower dose than MTD defined in Schedule A will be used as the starting dose of Schedule B .

After assessing the safety and tolerability of AZD7762 according to Schedule B, the highest dose demonstrated to be tolerable in Schedule B will be administered to three more patients to investigate the effect of AZD7762 on the pharmacokinetics of gemcitabine. In this case, the study will start with Cycle 1 (without Cycle 0), and the patients will be given only gemcitabine at the first dosing of Cycle 1. From the second dosing onwards, the patients will receive gemcitabine in combination with AZD7762 to compare the pharmacokinetics after single-agent therapy of gemcitabine with that after combination therapy with gemcitabine and AZD7762.

4.2.2 Justification of the starting dose

The starting dose of 4 mg/m^2 (6-mg absolute dose) for this study is the same that in the preceding overseas study D1040C00002. The starting dose for the study D1040C00002 was selected as it was approximately 1/100th of the serious toxicity dose (STD) in the dog (362 mg/m^2), and less than 1/10th of the dose producing minimal myocarditis in the most sensitive species (male rats at 42 mg/m^2). No NOEL for this effect had been established in male rats, but the NOEL in female rats was 130 mg/m^2 and this effect was not seen in dogs. This adverse event, although irreversible, can be monitored sensitively with troponin T levels in the clinic. The proposed starting dose is also comparable to the dose producing minimal, transient change in cardiac contractility in the conscious dog (contractility effects were seen at 5 mg/m^2) and less than 1/10th of the dose that produced even transient blood pressure change.

Pre-clinically, a good PK/PD correlation was seen. Extrapolating to human exposure, sustained concentrations associated with pharmacodynamic activity should first be evident at 6 mg/m^2 (approximates doses of 9 to 12 mg in this study) with ED_{50} to ED_{100} for abrogation of Chk1 pathway at doses 15 to 30 mg/m^2 (approximate doses of 27 to 54 mg in this study). Minimal, short-lived changes in diastolic blood pressure were not seen until a dose of 152 mg/m^2 in conscious, instrumented dogs, although minimal, reversible decreases in contractility were evident for <4 h following a dose of 5 mg/m^2. Absolute doses will be used

in the protocol as the same as the ongoing study D1040C00002 (Grochow et al 1990, Baker et al 2002).

Prolonging infusion time reduces maximal plasma concentration, which should translate to a lower probability of any changes in ejection fraction at higher doses Based on the association of contractility changes with C_{max} exposures, infusion time for the GLP toxicology studies has been performed with 1-hour infusions and AZD7762 will be infused over one hour in this Phase I study.

In the ongoing overseas study D1040C00002, the starting dose of gemcitabine was 750 mg/m^2 (75% dose level of the standard dose). After the safety of the starting dose was confirmed, the dose of gemcitabine was increased to a full standard dose (1000 mg/m^2) at second dose level As of 9 March 2009 (preliminary and unvalidated), since tolerability of the AZD7762 21 mg/gemcitabine 1000 mg/m^2 was confirmed in ongoing study D1040C00002, 1000 mg/m^2 is selected as the starting dose of gemcitabine in this study.

5. SUBJECT SELECTION CRITERIA

Subject population should be selected without bias. Investigator(s) must keep a record of subjects who entered pre-trial screening but were never enrolled eg, subject screening log. Each subject must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

5.1 Inclusion criteria

For inclusion in the study subjects must fulfil the following criteria.

1. Provision of written informed consent

2. Male or female age ≥20 and <75 years

3. Histologically or cytologically confirmed malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.

4. WHO performance status of 0 or 1 (see Appendix D)

5. Patient and tumor type must be suitable for treatment with weekly standard gemcitabine. Prior gemcitabine therapy is permitted.

6. Consent for provision of an archival tumor specimen for analysis of tumor characteristics

7. Available for hospitalization at least by Cycle 1 Day 15 (or Day 22 in Schedule B and the “PK expansion group”)

For inclusion in the optional germline genetic component of the study, patients must provide specific informed consent. If a patient declines to participate in the optional germline genetic component of the study, there will be no penalty to the patient. The patient will not be excluded from the therapeutic study described in this Clinical Study Protocol. See Appendix I for further information on optional genetic germline analysis.

5.2 Exclusion criteria

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

1. Inadequate bone marrow reserve as demonstrated by absolute neutrophil count (ANC) $\leq 1.5 \times 10^9$/L, platelet count (PLT) $\leq 100 \times 10^9$/L, or hemoglobin (HB) ≤ 9 g/L

2. Inadequate liver function as demonstrated by serum total bilirubin ≥ 1.5 x upper limit reference range (ULRR), or alanine aminotransferase (ALT), aspartamine aminotransferase (AST), or alkaline phosphatase (ALP) ≥ 2.5 x the ULRR (≥ 5 x the ULRR in the presence of liver metastases)

3. Impaired renal function, defined by creatinine ≥ 1.3 times the upper limit of normal (ULN) and creatinine clearance <50 mL/min (either measured or derived by Cockcroft-Gault method)

4. Quantitative troponin T CTCAE ≥grade 1 elevation (see Section 7.3.5.1)

5. Any evidence of severe or uncontrolled systemic diseases including known cases of Hepatitis B or C or human immunodeficiency virus (HIV). Screening for chronic conditions is not required, although patients known to have such conditions at screening should not be included

6. Stage II, III, or IV cardiac status, according to NYHA classification; recent history (ie, within 6 months) of coronary artery disease or arteriosclerotic cardiovascular disease (angina, myocardial infarction [MI])

7. Any prior anthracycline treatment

8. Resting LVEF <55% measured by ECHO

9. Mobitz type 2 second degree heart block. This requirement may be eliminated pending review of dose escalation safety data.

10. PR interval greater than 217 msec

11. Use of any known potent negative inotropic drug

    – calcium channel blockers: verapamil, diltiazem;

- beta-blockers: metoprolol, propranolol, atenolol, bisoprolol, carvedilol, timolol, sotalol, esmolol;

- anti-arrhythmics Class I): disopyramide, procainamide, mexiletine; (Class III): amiodarone; (Class IV): adenosine; miscellaneous: acetylcholine, propofol, nitric oxide, TNF, interleukine-1, interleukine-2

12. Therapeutic radiotherapy within the previous 4 weeks, or unresolved acute or subacute toxicities from prior radiotherapy. Localized, palliative radiotherapy must have been completed ≥2 weeks prior to first study treatment

13. Brain metastases or spinal cord compression, unless surgically removed and/or irradiated at least 4 weeks before study entry and stable without steroid treatment for ≥1 week

14. Pregnancy or breast-feeding. Women of childbearing potential must have a negative pregnancy test prior to start of study treatment

15. Male patients who do not intend to take any contraceptive measures during the study and during 6 months from the last day of the study treatment

16. Any severe concomitant condition which, in the opinion of the Investigator, makes it undesirable for the patient to participate in the study or which could jeopardize compliance with the protocol

17. Prior severe reaction to gemcitabine therapy (NB prior gemcitabine therapy is not an exclusion criteria)

18. Interstitial pneumonia or pulmonary fibrosis clearly documented in chest X-ray picture

19. Last dose of systemic anti-cancer therapy and all investigational agent received within 14 days prior to first dose of AZD7762. If sufficient wash-out time has not occurred due to schedule or PK properties, a longer wash-out period will be required according to expected time to anti-tumor affect, known duration and time to reversibility of drug related adverse events or at least 5 times the half-life to ensure no PK interaction, as agreed upon by AstraZeneca and the Investigator.

20. Unresolved toxicity greater than CTCAE grade 1 from previous anti-cancer therapy (excluding neurotoxicity or alopecia) or incomplete recovery from previous surgery, unless agreed by AstraZeneca and the Principal Investigator and documented

21. Major surgery within 4 weeks prior to first dose of study treatment

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

5.3 Optional genetic studies

An optional blood sample for retrospective genetic analysis of genes that may affect the absorption, distribution, metabolism, excretion or clinical outcomes to AZD7762 will be obtained only from consenting patients. Samples from patients participating in this study are part of a larger genetics program within AstraZeneca for this drug. A patient's consent for this optional sample is not a requirement for enrollment in the main study.

5.4 Procedures for handling incorrectly included subjects

Subjects that do not meet the inclusion/exclusion criteria for a study should not, under any circumstances, be enrolled into the study– there can be no exceptions to this rule.

Where subjects that do not meet the study criteria are enrolled in error, or where subjects subsequently fail to meet the criteria for the study post enrolment, the procedures included in the protocol for the discontinuation of such subjects must be followed (see Sections 5.5.2 and 5.5.3).

Once the error is identified a discussion must occur between the AZ Study Team Physician and the Investigator regarding whether to continue or discontinue the subject from the study. The AZ Study Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the subject should have their therapy stopped and be discontinued from the study

5.5 Withdrawal of subjects

5.5.1 Criteria for discontinuation from the study

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject are:

- Voluntary discontinuation or disagreement to give consent to the continued study treatment (before start of Cycle 2) by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Risk to subjects as judged by the investigator and /or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- Incorrectly enrolled subjects
- Subject lost to follow-up
- Lack of recovery to ≤CTCAE grade 2 within 4 weeks from onset of adverse events
- Disease progression

- When pregnancy becomes to be known

5.5.2 Procedures for discontinuation of a subject from the study

A patient that discontinues should always be asked about the reason(s) for discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 7.3.3 and 7.3.4).

5.5.3 Procedures for discontinuation from analysis of archival tumor sample (genetic and protein)

Subjects who discontinue from the main study should always be asked specifically whether they are withdrawing or continuing their consent for this linked tumor genetic and protein research. It must be established whether the subject:

- Agrees to the archival tumor samples and any DNA extracted from the samples being kept for genetic analyses in the future
- Agrees to the archival tumor samples being kept for protein analyses in the future
- Withdraws consent for the archival tumor samples to be kept for genetic and/or protein analyses in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses

The principal investigator is responsible for providing written notification to AstraZeneca of any subject who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the Investigator Site File. Requests by the subject to withdraw from the genetic research should be made through the principal investigator, who will inform the appropriate contacts within AstraZeneca.

Refer to Appendix I for procedures for discontinuation from the optional germline genetic part of the study.

6. STUDY CONDUCT

6.1 Restrictions during the study

Due to the experimental nature of AZD7762, the following conditions will be required of patients during their participation in this study (from the time they sign the consent form):

For further information regarding concomitant medications refer to Section 6.5.

Female patients must:

- be using an acceptable method of contraception (oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, intrauterine device, tubal ligation or abstinence) from the time they sign the consent form to 6 months after the last infusion of AZD7762 or
- be at least 1-year post-menopausal, or have had no menses for 12months or
- be surgically sterile to prevent pregnancy.

Male patients must

- be surgically sterile or using an acceptable method of contraception from the time they sign the consent form to 6 months after the last infusion of AZD7762

All patients

- must not use concomitant drug of any known negative inotropic drug. Refer to list under exclusion criteria Section 5.2 #11.
- recommend use SPF ≥30 sunblock for 48 hours after every dose of AZD7762, and avoid the use of sun-beds or extensive sun exposure during the study.

6.2 Subject enrolment

The centralised registration centre will manage and keep the registration code centrally and electronically. The name and contact of centre are as follows:

Name: AZD7762 Centralised Registration Centre (AstraZeneca K.K.)

Fax: 06-6453-7802

Office hours: 9:30 – 17:30, Mon. – Fri.

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

The investigator(s) will allocate the enrolment code (E-code) to each patient after the written informed consent will be obtained. The E-code (EXXXXYYY) consists of a 4-digit centre number (XXXX) and a 3-digit serial number (YYY, starting with 001) issued by study centre in order of informed consent taken. For centre number, see Supplement A "Investigators and Study Administrative Structure".

The investigator(s) will perform an enrollment medical examination after the written informed consent will be obtained, and send the "Registration Notification" to the AZD7762 Centralised Registration Centre by fax (both eligible and ineligible) after the confirmation of patient's eligibility according to the results of screening tests. The AZD7762 Centralised Registration Centre will reconfirm the patient eligibility, and if eligible, the AZD7762

Centralised Registration Centre will register the patient and send by fax the "Registration Conformation Form" to the investigator(s). If ineligible, the AZD7762 Centralised Registration Centre will send by fax the "Registration Conformation Form" that documented ineligible to the investigator(s).

If a patient is not evaluable, an additional patient should be entered in that dose level (see Section 4.1.1).

If a patient discontinues from the study the E-code will not be re-used and the patient will not be allowed to re-enter the study.

6.3 Blinding and procedures for unblinding the study (Not applicable)

This is an open-label study therefore this section is not applicable.

6.4 Treatments

6.4.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer	Formulation number
AZD7762	Aqueous solution - 6 mg/mL	AstraZeneca	F13427

AZD7762 will be manufactured by AstraZeneca and supplied as 7 mL of aqueous solution at 6 mg/mL in single-dose vials. Study treatment provided for the study may not be used for any other purpose or by anyone other than the patients enrolled in this study.

6.4.2 AZD7762 Dose preparation

As with other potentially toxic anticancer agents, care should be used in the handling and preparation of infusion solutions prepared from AZD7762 injections. The use of gloves is recommended.

AZD7762 must be filtered before preparation in order to remove particulate matter. Inspect vial contents for particulate matter and repeat inspection when drug product is withdrawn from vial into syringe. AZD7762 must be diluted prior to infusion. AZD7762 is to be reconstituted with saline solution prior to intravenous injection. AZD7762 will be mixed in 250 mL of diluent. For detail, see the instructions for reconstitution, dose calculations, drug storage and handling provided by AstraZeneca K.K.

6.4.3 Gemcitabine dose preparation

Gemcitabine from commercial supply will be used for this study. See the package insert for the properties and preparation of infusion solutions.

6.4.4 Doses and treatment regimens

Gemcitabine will be administered as a 30-minute IV infusion. AZD7762 will be administered as a 60-minute IV infusion. Subsequently, the gemcitabine infusion will be administered followed immediately by AZD7762. For the patients in the "PK expansion group", only gemcitabine will be administered on Cycle 1, Day 1, AZD7762 will be administered from Cycle 1, Day 8. See Table 5 for the planned doses to be utilized in this study.

If the gemcitabine dose is omitted, no AZD7762 should be administered.

6.4.4.1 Planned dose levels

Table 5 Planned dose levels of AZD7762 and gemcitabine that may be explored

Dose Level	Dose of AZD7762 [b]	Dose of gemcitabine [c]	Number of Vials of AZD7762 required
-1[a]	3 mg	1000 mg/m^2	1
1	6 mg (starting dose)	1000 mg/m^2	1
2	9 mg	1000 mg/m^2	1
3	12 mg	1000 mg/m^2	1
4	18 mg	1000 mg/m^2	1
5	24 mg	1000 mg/m^2	1
6	36 mg	1000 mg/m^2	1
7	48 mg	1000 mg/m^2	2
8	72 mg	1000 mg/m^2	2
9	96 mg	1000 mg/m^2	3

a If Dose Level 1 PK information indicates exposures significantly higher than predicted, or DLT occurs, Dose Level -1 may be explored

b Intermediate dose levels to those presented may be used if appropriate (eg, 25% dose escalations). This table is intended as an example for guidance only.

c 100% of labelled gemcitabine dose. From Cycle 2 onwards in each of these dose levels, the gemcitabine dose for a cycle may be reduced in individual patients if necessary, based on the Investigators assessment of tolerability during the previous cycle(s) (see Section 6.4.4.3).

NB. The dose level may exceed Dose Level 9 if PK and safety criteria allow. See also Figure 3 for the dose escalation decision flow diagram.

Within each dose level the single agent AZD7762 dose will be the same as the combination AZD7762 dose.

6.4.4.2 Duration of treatment

Once a dose level has been completed, the patients on that dose level who are, in the Investigator's opinion, continuing to benefit and have not experienced cardiac dose-limiting

toxicity (see Section 4.1.6) during Cycle 1 (or any other untolerable toxicity), may continue on the study medication administered in combination with gemcitabine until protocol completion if the patient give consent to the continued study treatment. Patients may receive treatment as long as they are benefiting from treatment, there is no evidence of disease progression, they meet no other withdrawal criteria and they continue to receive gemcitabine therapy

Patients who withdraw from study treatment prior to progression will be followed for safety up to 30 days, where possible, after last administration of AZD7762 to monitor for any adverse events.

6.4.4.3 Rules for dose adjustment and omission of gemcitabine

Commencing rules for gemcitabine administration:

- ANC $\geq 1.0 \times 10^9$/L
- PLT $\geq 100 \times 10^9$/L

A substantial fraction of patients are expected to have AEs associated with gemcitabine that may mandate reduction or omission of a weekly gemcitabine dose. These dose reductions will not necessarily be considered dose-limiting toxicity for the combination (unless DLT criteria are met, refer to Section 4.1.6). As a result of dose adjustment of Gemcitabine, however, if the ratio of the actual dose to the planned dose in a cycle is less than 75%, the patients will be considered as non-evaluable patients and new subjects will be included for the replacement (see Section 4.1.2). Gemcitabine dose adjustments will be made according to the following. Patients receiving therapy should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. Gemcitabine dose adjustment for haematological toxicity is based on the neutrophil and platelet counts.

- Cycle 1:
  Table 6 and Table 7 should be followed in principle. If the event constitutes DLT, however, the treatment should be held according to the regulations in Section 4.1.6
- Cycle 2 onwards:
  Package insert and standard procedure of the site should be followed

Table 6 Recommended gemcitabine dose reduction guidelines within a cycle for hematologic toxicity

Absolute neutrophil count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
≥1000	and	≥100,000	100
500-999	or	50,000-99,000	75
<500	or	<50,000	Hold

Table 7 Recommended gemcitabine dose reduction guidelines within a cycle for non-hematologic toxicity

CTCAE grade	% of full dose
0 to 2 (and grade 3 nausea/vomiting)	100
3 (except nausea/vomiting)	50 or hold [a]
4	hold

a. Decision will depend on the type of non-hematological toxicity seen, and the judgement of the Investigator and AstraZeneca Study team Physician

Between-cycle gemcitabine dosage reduction guidelines

During Cycle 1 patients will receive the assigned gemcitabine dose (refer to Table 5), with dose modifications during the cycle if necessary (refer to Table 6 and Table 7). From Cycle 2 onwards, the gemcitabine dose for a cycle may be reduced in individual patients if necessary, based on the Investigator assessment of tolerability during previous cycle(s). Cycle gemcitabine dose may be reduced to 750 mg/m^2 if two or more doses in the previous cycle were omitted or modified. A second cycle gemcitabine dose reduction to 600 mg/m^2 is also permitted if necessary, based on the Investigator assessment of tolerability of 750 mg/m^2 during previous cycle(s). Refer to Section 6.4.4.4 for dose adjustment guidelines for AZD7762.

Gemcitabine cycle dosage may be subsequently readjusted upwards (eg, from 600 mg/m^2 to 750 mg/m^2, or 750 mg/m^2 to 1000 mg/m^2) if a patient tolerated all doses in the previous cycle.

Adequate supportive care and pre-medication will be allowed. This includes standard pre-treatment for gemcitabine with anti-emetics.

6.4.4.4 Rules for dose adjustment of AZD7762

Intra-patient dose adjustments of AZD7762 (increases or reductions) may be permitted according to the rules detailed below, only after discussion and agreement of individual patient situations between the Investigator and the AstraZeneca K.K. Study Delivery Team Physician.

Intra-patient dose increases of AZD7762

One dose level increase of AZD7762 is permitted from Cycle 3 onwards, only to the next sequential higher dose level already known to be tolerable in a subsequent complete cohort (ie, that cohort contains at least 3 evaluable patients and dose escalation has already been approved). Upward titration of both AZD7762 and gemcitabine must not be made simultaneously. A dose increase of gemcitabine should precede that of AZD7762.

Intra-patient dose reductions of AZD7762

If an event of CTCAE grade 3 or greater occurs during the study treatment and it is not ruled out that AZD7762 is responsible as judged by the investigator(s), the dose of AZD7762 may

be reduced by one dose level (if the dose is 6 mg, reduce it to the dose level of 3 mg). However, if the event constitutes DLT, the treatment should be held following Section 4.1.6.

As far as it is not judged that the event is caused by AZD7762, dose reductions of gemcitabine should occur first, following the details in Section 6.4.4.3 (ie, initial cycle dose reduction of gemcitabine to 750 mg/m^2, and then next cycle dose to 600 mg/m^2). If no tolerability improvements are seen despite dose reduction of AZD7762 and gemcitabine, then the patient should be withdrawn. As with gemcitabine, AZD7762 cycle dosage may be subsequently readjusted upwards (only to the previously assigned dose level) if a patient tolerated all doses in the previous cycle.

If neither of the drugs is determined to be responsible for the event, doses of both gemcitabine and AZD7762 may be reduced. In this case, gemcitabine dose that is decreased to the dose level defined in Section 6.4.4.3, and AZD7762 dose that is one level lower will be used.

AZD7762 must only be administered following gemcitabine with the exception of Cycle 0. If the gemcitabine dose is omitted for any reason, then the AZD7762 dose must also be omitted.

6.4.5 Additional study drug (Not applicable)

6.4.6 Labelling

Each container of AZD7762 will have an investigational-use label permanently affixed to the outside and will be labelled in accordance with local regulations, stating that the drug is for investigational use only and should be kept out of reach of children. Labels for AZD7762 will include at least the following:

- Name of sponsor (AstraZeneca)
- Study number D1040C00008
- Aqueous solution for IV dosing, 7 mL of 6 mg/mL AZD7762
- Batch number
- Storage conditions
- Directions for use
- “for clinical study use only”
- “keep out of reach of children”

The investigational product will be supplied as a concentrate for solution for infusion. Study site dispensary staff will dilute and dispense the investigational product according to the scheme.

6.4.7 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. The vials and the vehicle should be stored in their original packaging until use. For further information, Investigators should refer to the investigational product label. Instructions for reconstitution, dose calculations, drug storage and handling are provided as Guidance for the Pharmacist prior to study initiation.

6.5 Concomitant and post-study treatment(s)

Any medication that is considered necessary for the patient's safety and well-being, eg, anti-emetics, EPO, may be given at the discretion of the investigator(s) with the exceptions noted in the Exclusion Criteria (see Section 5.2) and below. The patient must be instructed that no additional medication will be allowed without the prior consent of the investigator. The administration of all medication (including investigational products, prescription, non-prescription or over-the-counter medication) must be recorded in the appropriate sections of the CRF.

G-CSF should not be routinely administered except beyond Cycle 1, and only if it is deemed necessary by the Principal Investigator. Concomitant use of medications that are primarily metabolized via CYP2C8 should also be avoided, unless clinically essential. Concurrent thoracic radiotherapy should be avoided.

Refer to the restrictions in Section 6.1 for other medications excluded during the study period.

Concomitant medications should be re-assessed at each treatment day.

6.5.1 Pre-medication

Pre-medication for gemcitabine will be left to the discretion of the Principal Investigator in accordance with local practice.

6.6 Treatment compliance

Doses of AZD7762 and gemcitabine will be administered in the clinic as per the protocol schedule and normal clinical practice. Patients may be discontinued from the study if severe non-compliance occurs as judged by the investigator and/or AstraZeneca.

The administration of all medication (including AZD7762/gemcitabine) must be recorded in the appropriate sections of the Case Report Forms.

6.6.1 Accountability

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

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the institution until the return of all unused study drug to AstraZeneca. For details, to refer AstraZeneca will provide the study documents

'Procedures for drug accountability' and 'Procedures for drug storage', which AZ K.K. will provide for medical center.

7. COLLECTION OF STUDY VARIABLES

7.1 Recording of data

The principal investigator/sub-investigator will record data on the observations, tests and assessments specified in the protocol on the CRFs provided by AstraZeneca. The CRF will be accompanied with 'Instructions for the Investigator', which should be followed to record study data in the CRF and to change data incorrectly recorded.

The investigator will ensure that all data collected in the study are provided to AstraZeneca. He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the paper Case Report Form or electronic Case Report Form and according to any instructions provided.

7.1.1 Reporting of genetic and protein analysis results

Results from the genetic and protein analysis of p53 and MDM2 (and any other genes analyzed) in blood and archival tumor samples will not be reported within the clinical study report. AstraZeneca will not provide individual results to subjects, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The subject's DNA will not be used for any purpose other than those described in the study protocol.

Individual subjects will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the subject's name nor any other personal identifiers will appear in any publication or report.

7.2 Screening and demography procedures

Each patient will undergo an enrollment medical examination in the 28 days prior to the first study treatment (Cycle 0, Day 1). This will consist of:

- Recording of demographic data - date of birth, sex, height, weight, race, tumor type
- A standard past and current medical history including current symptoms
- Physical examination
- A resting blood pressure, pulse and body temperature measurement.
- Standard hematology, clinical chemistry, urinalysis, quantitative troponin T, CPK and brain natriuretic peptide

- Resting 12-Lead electrocardiogram (ECG)
- ECHO
- Baseline tumor evaluation (RECIST) within 28 days prior to first dose of AZD7762. Note: a second baseline RECIST evaluation will be obtained within 5 days prior to initiating combination treatment with AZD7762 and gemcitabine (ie, between day 10 and 15 of cycle 0), only if not previously obtained within 28 days of first combination dose of AZD7762 and Gemcitabine (Cycle1, Day 1).
- Urine or serum pregnancy test (pre-menopausal females only)
- WHO Performance status (Appendix D)
- Recording of concomitant medications

Tumor assessment data obtained within 28 days before the fist administration of AZD7762 may be utilized for study once patient provides consent even though the data obtained before informed consent (no invasive or study-specific screening assessments will be performed until consent is obtained).

7.2.1 Follow-up procedures

Each patient will be followed for 30 days after the last administration of AZD7762 in order to assess adverse events and concomitant medications.

7.3 Safety

It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

7.3.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Any deterioration of the disease targeted in the study and associated symptoms should not be regarded as an adverse event as far as the deterioration can be anticipated.

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

7.3.2 Definitions of serious adverse event

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

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

For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and is reported in an expedited manner. Any organism, virus or infectious particle (for example prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

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

7.3.3 Recording of adverse events

AEs and SAEs will be collected throughout the study and will be recorded from the time of informed consent until 30 days after last dose of study treatment. AEs will be followed up to resolution or for 30 days after the last administration of study treatment.

Variables

The following variables will be recorded in the CRF for each AE; description of the AE, the date when the AE started and stopped, CTC grade, whether the AE is serious or not, causality rating (yes or no), action taken with regard to investigational product, whether any treatment is given for the AE or not, AE caused subject to discontinue study and outcome.

Causality

The Investigator will assess causal relationship between Investigational Product/gemcitabine and Adverse Events, and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product/gemcitabine”. Causal relationship in cases where the disease under study has deteriorated due to lack of effect will be classified as no reasonable possibility.

For SAEs causal relationship will also be assessed for study procedure. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as “yes”.

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

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs when any of the following criterion occur: 1) Serious Adverse Event (SAE) criterion is fulfilled, 2) the laboratory / vital signs / LVEF abnormality causes the subject to discontinue from the study treatment, 3) the investigator believes that the abnormality should be reported as an AE, or 4) the abnormal lab value/vital sign or LVEF fulfils a DLT criterion (unless clearly due to disease progression), or 5) treatment is administered. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Clinically relevant deterioration in non-protocol-mandated measurements will be reported as AE(s).

Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value).

Follow-up of unresolved adverse events

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

Worsening of disease related symptoms

Worsening of disease related symptoms can be thought of as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease (or symptoms of the disease). Expected progression of the disease being studied, including signs and symptoms of the progression, should not be reported as an AE unless more severe in intensity or more frequent than expected for the patient's condition.

Any events that are unequivocally due to progression of the disease under study must not be reported as an AE.

Lack of efficacy

When there is a deterioration in the condition for which the study treatment is being used, 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 study treatment contributed to the deterioration, the deterioration would be considered a lack of efficacy and not an AE.

New Cancers

The development of a new cancer should be regarded as a SAE. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study.

Deaths

All deaths that occur during the study, or within the protocol defined follow-up period after the administration of the last dose of study treatment, 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 a SAE.

Where death is not due (or not clearly due) to progression of disease under study, the AE causing the death must be reported to AstraZeneca as a SAE within 1 day (in this section, within 1 day is defined as "immediately but no later than the end of the next business day"). 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.

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 AstraZeneca within the timeframes specified in Section 7.3.4.

Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 1.2, Procedures in case of overdose, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

Pregnancy

Should a pregnancy occur, the subject should immediately be withdrawn from the study and it must be reported in accordance with the procedures described in Section 1.3, Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. If the partner of a male patient becomes pregnant, this should also be reported.

7.3.4 Reporting of serious adverse events

Investigators and other site personnel must inform (emergency report) appropriate AstraZeneca KK representatives of any SAE that occurs at his or her site in the course of the study within 1 day (in this section, within 1 day is defined as "immediately but no later than the end of the next business day") of when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the study treatment or to the study procedure(s). The Principal Investigator must provide detailed information to AstraZeneca in writing within 4 calendar days of the initial report. The Principal Investigator must notify the serious adverse events in writing to the head of the study site immediately.

Follow-up information on SAEs must also be reported to AstraZeneca KK by the investigator(s) within the same time frames. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above.

The following information is required in the initial SAE report to AstraZeneca KK from the investigator(s); study code, site number, Enrolment code, adverse event, seriousness, start date. The following detailed information must be sent to AstraZeneca KK as soon as it becomes available;

Severity, outcome (including stop date, if available), causality (investigational product and if applicable any other concomitant drug), date when a non-serious AE became serious, withdrawal of study treatment, treatment of adverse event, concurrent therapy (except for treatment of AE), concurrent medication (including pre-study medication if the causality of the AE cannot be assessed), date of birth, sex, other current illnesses, relevant medical history and if applicable, date and course of death.

For all SAEs, the AstraZeneca representative will inform the AstraZeneca Drug Safety Department of it by day 1 and will work with the investigator(s) to compile all the necessary information and ensure that the Drug Safety Department receives a report within 4 calendar days.

In addition AstraZeneca will provide details of any unexpected serious adverse drug reactions or expected fatal or life-threatening serious adverse drug reactions reported with regard to the test product in this study or other compound available overseas in which the active ingredient is known to be equivalent to the test product, to the Head of the study site, Principal Investigator and the regulatory agency. The Head of the study site must submit a written report to the IRB providing the details of all adverse event case(s) reported by AstraZeneca.

7.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis parameters should be performed at a local certified clinical laboratory at the times listed in the study plan (Table 1 [or Table 3 for Schedule B and the "PK expansion group"]). Hematology and chemistry labs may be obtained up to 3 days prior to Cycle 0, Day 1 (Visit 2) (Schedule B: Cycle 1, Day 1 [Visit 4]). If screen data are obtained during this time window, the screen

data may be used as the data for Visit 2 (or Visit 4 for Schedule B and the "PK expansion group"). After the first dosing, hematology and chemistry labs may be obtained up to 1 day prior to the study dosing. Urinalysis and all tests at any visits without the study dosing may be obtained within ±2 days from the study visit.

The following laboratory variables will be measured:

Hematology

Reticulocyte count, leukocyte count (WBC), red cell count (RBC), hemoglobin (Hb), hematocrit (HCT), platelet count (PLT), absolute neutrophil count (ANC), mean cell volume (MCV), international normalized ratio (INR), activated partial thromboplastin time (APTT)

Clinical chemistry

Plasma glucose, serum sodium, blood urea nitrogen (BUN), serum calcium, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum alkaline phosphatase (ALP), serum total bilirubin, serum magnesium, serum potassium, serum albumin, serum creatinine, serum total protein, serum inorganic phosphate, cardiac markers*

* Cardiac markers: quantitative and qualitative troponin T and creatine phosphokinase (CPK) at the times indicated in the study plan (Table 1 [or Table 3 for Schedule B and the "PK expansion group"]), and brain natriuretic protein (BNP) only at baseline and in patients who develop symptoms of dyspnea or congestive heart failure

Urinalysis

Human chorionic gonadotrophin (HCG)*, specific gravity, glucose, protein, bilirubin, ketones, blood, pH

* Pre-menopausal females only must give a sample of the first urine passed at Visit 1 for a pregnancy test to be performed, this test may also be performed on a serum sample

For blood volume see Section 8.1

7.3.5.1 Troponin T Measurements

For timing of individual measurements refer to study plan (Table 1 [or Table 3 for Schedule B and the "PK expansion group"]). Pre-dose qualitative troponin T will also be measured, and dosing will not proceed (for Cycle 0, Cycle 1, and the first dose of all following cycles), until it has been confirmed that the patient does not have a positive (≥0.1 ng/mL) elevation.

Troponin T sample time windows:

- Pre-dose quantitative and qualitative samples can be obtained ≤ 2 days prior to visit (or ≤3 days prior to Cycle 0, Day 1 [Cycle 1, Day 1 for patients in Schedule B and the "PK expansion group"])

- Quantitative troponin T samples 4 hours and 8 hours after the start of the AZD7762 infusion can be obtained ±1 hour relative to scheduled timepoint

- Quantitative troponin T samples 24 hours, 48 hours or 72 hours after the start of AZD7762 infusion can be obtained ± 2 hours relative to scheduled timepoint

7.3.6 Physical examination

Physical examination will be performed at screening visit (Visit 1) The investigator will exam general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, lungs, abdomen and neurological.

7.3.7 ECG

For timing of individual measurements refer to study plan (Table 1 [or Table 3 for Schedule B and the "PK expansion group"]).

Twelve-lead ECGs will be obtained after the patient has been lying down for 5 minutes.

- Heart rate, QRS duration, PR interval, QT interval, sinus rhythm and overall evaluation

7.3.8 Vital signs

Blood pressure, pulse, body temperature and weight are to be taken routinely with each visit through Cycle 1, then at the beginning of each cycle (Table 1 [or Table 3 for Schedule B and the "PK expansion group"]).

- Cycle 0 Day 1: prior to AZD7762, and at 0.5 (during infusion), 1, 1.5, 2, 3, and 4 h after the start of AZD7762 infusion (body temperature to be taken only prior to AZD7762 in fusion)

- Cycle 1, Day 1: prior to gemcitabine infusion, prior to AZD7762, and at 0.5 (during infusion), 1, 1.5, 2, 3 and 4 h after the start of AZD7762 infusion (body temperature is to be taken only prior to gemcitabine infusion)

7.3.9 Other safety assessments

7.3.9.1 Left ventricular ejection fraction (LVEF)

Resting LVEF will be measured by ECHO. The method of measurement must be the same in the individual patient. For timing of individual measurements refer to the study plan (Table 1 [or Table 3 for Schedule B ant the "PK expansion group"]). If EF declines by ≥10 points from baseline to a value <50% or there is an absolute decrease of ≥16 % in an EF value that was above 50% for ≥24 hours, follow up must be repeated the following day. ECHO will be performed when possible if grade 2 or more decreases in BP occur.

7.3.9.2 Creatinine clearance

The following formula (Cockcroft and Gault equation) will be used to estimate creatinine clearance (a measured value for creatinine clearance may instead be used if appropriate, eg, by 24 h urine measurement).

- Males: Creatinine clearance (mL/min) = $\frac{\text{weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mg/dL)}}$

- Females: Creatinine clearance (mL/min) = $\frac{\text{weight (kg) x (140 - age) x0.85}}{\text{72 x serum creatinine (mg/dL)}}$

7.3.9.3 Chest X-ray

For timing of individual measurements refer to study plan (Table 1 [or Table 3 for Schedule B and the "PK expansion group"]). If chest CT scan is performed as a part of tumor evaluations during the time window of chest X-ray, chest X-ray is not mandatory.

7.4 Efficacy

7.4.1 Anti-Tumor Activity

Information on all tumor lesions will be obtained at baseline by radiological techniques. Patients enrolled in the study with measurable tumors, will have tumor response evaluated using RECIST criteria (for details refer to Appendix G) according to the study plan (Table 1 [or Table 3 for Schedule B and the "PK expansion group"]). Each lesion that is measured at baseline must be measured by the same method throughout the study so that the comparison is consistent. In patients who had a repeat baseline scan taken on day 10-15, this scan is considered baseline for comparison with subsequent follow-up assessments. If a response is seen a confirmation scan after 4-6 weeks is required (for definition of response refer to Appendix G). Anti-tumor activity in patients with unmeasurable disease will only be noted. Investigator assessment of overall response will be collected as determined from baseline evaluation, duration of response or stable disease, and whether response is confirmed.

7.5 Pharmacokinetics

7.5.1 Collection of biological samples

See Table 1(or Table 3 for Schedule B and the "PK expansion group") and Appendix E for additional information on the collection and processing of biological samples.

For blood volume see Section 8.1.

7.5.2 Determination of drug concentration in biological samples

Drug concentration of AZD7762 in plasma will be determined by using high-performance liquid chromatography with tandem mass-spectrometric detection (HPLC-MS-MS).

will determine gemcitabine concentrations using a validated HPLC-MS-MS method.

Metabolite analysis will be performed by AstraZeneca (or a designee laboratory if appropriate).

The methods used will be referred to in the clinical study report (CSR).

7.6 Pharmacodynamics

7.6.1 Archival tumor biopsy

All patients will be required to provide consent to supply a sample of their archival tumor material for entry into this study. It is accepted that it may not be possible to obtain all samples prior to commencement of study related treatment. It is also accepted that it may not be possible to obtain a sample for every patient (eg, if sufficient sample does not exist).

See Appendix F for information on the collection of the archival tumor biopsies.

7.6.2 Analysis of archival tumor sample

Expression of p53 (and other relevant genes, eg, MDM2) may also be measured in biopsy samples.

7.7 Pharmacogenetics

7.7.1 Archival tumor specimen for genetic and protein analysis

All patients will be required to provide consent to obtain a sample of their archival tumor material for entry into this study. The tissue obtained in Section 7.6.1 may be used for both protein analysis (eg, p53 and MDM2 protein expression), and also genetic analysis of p53 (and other relevant genes). In order to perform this genetic analysis, DNA will be extracted from the tumor archival samples. Evaluation of genes in DNA damage and repair pathways, such as Chk1, Chk2, p53, p21 may also be undertaken.

Details of the collection of archival tumor biopsies are presented in Appendix F (Handling and shipment of pharmacodynamic samples).

7.7.2 Optional germline genetic analysis

As an optional component of the study patients will be asked to give consent to provide a blood sample for germline genetic analysis. Details of this are outlined in Appendix I (Optional Germline Genetic Research).

For blood volume see Section 8.1.

7.8 Health economics (Not applicable)

8. BIOLOGICAL SAMPLING PROCEDURES

8.1 Volume of blood

Table 8 and Table 9 represent the total volume of blood that will be drawn from each patient.

These volumes are intended as a guide and indicate maximums, additional safety blood samples may be required when clinically indicated.

Table 8 Maximum volume of blood to be drawn from each patient (screen to Cycle 1)

Assessment	Sample volume (mL)	n of samples			Total volume (mL)		
		Schedule A	Schedule B	PK expansion	Schedule A	Schedule B	PK expansion
PK AZD7762	1	21	0	9	21	0	9
Gemcitabine	3	0	0	12	0	0	36
Germline Genetic Sample (optional)	9	1	1	1	9	9	9
Safety							
Clinical chemistry (includes CPK)	6	6	5	5	36	30	30
Hematology	3	6	5	5	18	15	15
INR/APTT	2	1	1	1	2	2	2
Troponin T (quantitative and qualitative)	6	17	10	10	102	60	60
BNP	5	1	1	1	5	5	5
Total					193	121	166

Table 9 Maximum volume of blood to be drawn from each patient in each cycle after Cycle 2

Assessment		Sample volume (mL)	n of samples		Total volume (mL)	
			Schedule A	Schedule B/PK expansion group	Schedule A	Schedule B/PK expansion group
Safety	Clinical chemistry (includes CPK)	6	3	4	18	24
	Hematology	3	3	4	9	12
	Troponin T (quantitative and qualitative)	6	2	2	12	12
Total					39	48

8.2 Handling, storage and destruction of biological samples

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

Biological samples for future research will be retained at AstraZeneca R&D site for a maximum of 15 year following the finalisation of the Clinical Study Report. The results from future analysis will not be reported in the Clinical Study Report.

8.2.1 Storage and coding of DNA samples

The processes adopted for the coding and storage of archival tumor and blood samples for genetic analysis are important to maintain subject confidentiality.

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

The archival tumor and blood samples and data for genetic analysis in this study will be coded. The link between the subject enrolment code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

8.3 Labelling and shipment of biohazard samples

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

Any samples identified as Infectious Category A materials are not shipped and further samples taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

8.4 Chain of custody of biological samples

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

The principal investigator at each centre keeps full tractability of collected biological samples from the subjects while in storage at the centre until shipment and keeps documentation of receipt of arrival.

The sample receiver keeps full tractability of the samples while in storage and during use until used or disposed.

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

Samples retained for further use is registered in AstraZeneca bio bank system during the entire life cycle.

8.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of biological samples donated the samples will be disposed/destroyed, if not already analysed and documented.

If collection of the biological samples is an integral part of the study then the subject is withdrawn from further study participation.

If collection of the biological samples is a voluntary part of the study then the subject may continue in the study.

The principal investigator:

- Ensures subjects withdrawal of informed consent is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed/destructed and the action documented.

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

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

In the event that analysis/research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

9. ETHICAL AND REGULATORY REQUIREMENTS

9.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. The applicable regulatory requirements in Japan are Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications.

9.2 Subject data protection

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

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

9.3 Ethics and regulatory review

An Institutional Review Board (IRB) must approve the final study protocol, including the final version of the Informed Consent Form and any other written information to be provided to the patients and CRF. The head of the study site will ensure the distribution of these documents to the applicable IRB and the principal investigator to the sub-investigator(s) and study site staff.

The opinion of the IRB must be given in writing. The head of the study site must submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca before enrolment of any subject into the study.

The IRB must approve all advertising used to recruit patients for the study.

AstraZeneca must approve any modifications to the Informed Consent Form that are needed to meet local requirements.

The protocol must be re-approved by the IRB annually. The principal investigator must submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval. A valid contract between the medical institution and AstraZeneca Japan must be signed before the investigator can enrol any subjects into the study.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The distribution of any of these documents to the national regulatory authorities will be handled by AstraZeneca.

9.4 Informed consent

The principal investigator(s) at each centre will:

- Ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure that the subjects are notified that they are free to discontinue from the study at any time.
- Ensure that the subject are given the opportunity to ask questions and allowed time to consider the information provided.
- Obtain and document the subject's signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent Form is stored in the Investigator's Study File.
- Ensure a copy of the signed Informed Consent Form is given to the subject.

If any new information on the study medication becomes available which may influence the decision of the subject to continue the study, the investigator(s) must inform the subject of such information immediately, record this in a written form, and confirm with the subject if he or she wishes to continue the participation in the study. In addition, if the investigator(s) deem it necessary to revise the Informed Consent Form, they must revise it immediately

(Refer to Section 9.5). The investigator(s) must re-explain the subjects using updated Informed Consent Form even if although the subjects have already been informed of the new information verbally. Written informed consent to continue participation in the study must be provided separately.

9.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Co-ordinating Investigator and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment must be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented.

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used.

If an administrative change is required, such a change must be notified to or approved by each IRB according to local requirements

9.6 Audits and inspections

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

All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

10. STUDY MANAGEMENT BY ASTRAZENECA

10.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of

AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator

10.2 Training of study site personnel

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

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

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

10.3 Monitoring of the study

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

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, and that investigational product accountability checks are being performed.
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) incl. verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed/destructed accordingly, and the action is documented, and reported to the subject.

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

10.3.1 Source data

Source data are any data generated as a result of the subject's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records Original data recorded on the CRFs and regarded as source data are as follows.

1. Some assessments of inclusion and exclusion criteria

2. Some of demographic data (race)

3. Cause of death

4. Causality of AE

5. Reason for each concomitant medication

6. All of comments

7. Judgement of DLT

10.3.2 Direct access to source data in Japan

The Head of the institution and the principal investigator/sub-investigator will cooperate for monitoring and audit by AstraZeneca, and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the CRFs against source data before collecting the CRFs to ensure accuracy and completeness of documentation, and assure that the principal investigator/sub-investigator has submitted the CRFs to AstraZeneca. If the investigator wishes to amend the collected CRFs, the monitor will ensure that the principal investigator/sub-investigator has documented the amendment in writing (signed and dated) and provided this to AstraZeneca.

10.4 Study agreements

The principal investigator at each/the centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

Agreements between AstraZeneca and the Principal Investigator must be in place before any study-related procedures can take place, or subjects be enrolled.

10.4.1 Deviation from the clinical study protocol in Japan

The investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval based on its deliberations.

The investigator(s) will record all deviations from the protocol.

The principal investigator should submit a report to AstraZeneca K.K. and the head of the study site (and the IRB via the head of the study site), to notify any change which may give a significant impact on the conduct of the study or increase a risk to the patient.

The investigator(s) may deviate from or make a change to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval, only in the event of a medical emergency, e.g. it is only way to avoid an emergency risk to the patient. In such case, the principal investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to AstraZeneca K.K. and the head of the study site (and IRB via the head of the study site) as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca K.K. should be obtained via the head of the study site.

10.5 Study timetable and end of study

The end of the entire study is defined as ”the last visit of the last subject undergoing the trial”.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD7762

10.5.1 Planned duration of the study

Study period: June 2009 – July 2013
Registration period: June 2009 – July 2012

10.5.2 Discontinuation or suspension of the whole study programme

If AstraZeneca decides to prematurely terminate or suspend the study, the principal investigator, sub-investigator, the head of the institution, and regulatory authorities must receive written notification of the reasons for the premature termination or suspension.

The principal investigator/sub-investigator will immediately notify the decision to the subjects, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

10.5.3 Completion of the study

Upon terminating the study, the principal investigator/sub-investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the institution’s rules. The head of the study site who is informed of the termination by the investigator will provide a written notification of the results to the IRB and AstraZeneca.

10.5.4 Archiving of study documentation

(i) Study files

All study documents (including letters from AstraZeneca K.K.) should be retained in a file by the principal investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by AstraZeneca K.K.’s auditor, regulatory authorities, or IRB.

(ii) Period of record retention

The study site (and the principal investigator) will retain the essential documents specified in the ICH GCP (e.g., source document such as medical records, contract, signed consent form).

Essential documents must be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with AstraZeneca K.K.

However this is not always applied to those that are not preservable such as blood samples.

In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by AstraZeneca K.K., and the specific period and method of retention will be separately discussed between the study site and AstraZeneca K.K. AstraZeneca K.K. should notify the head of the study site in writing when the study related records are no longer needed.

The records should be managed by a responsible person appointed by the head of the study site.

11. DATA MANAGEMENT

The CRF and the clinical database is created in accordance with AstaZeneca standard operating procedures using existing project standards. CRF instructions are provided to sites for recording data. The data are entered, verified and cleaned and data sets prepared according to AstaZeneca procedures. The data management staff is responsible for conducting and/or overseeing the following information.

Data Management Plan (DMP)

The study DMP will describe the methods used to collect, check and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process.

Dictionary coding

Medical coding is done using the most current version of MedDRA and AstraZeneca Drug Dictionary.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool will be tested/validated as needed. External data reconciliation will be done with the clinical database as applicable.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with Patient Safety database.

Quality Control Process

Data Management performs the quality control of the data in accordance with the AstaZeneca SOPs. Clean file occurs when all process have been completed.

Genotype Data

Genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system, separate from the database used for the main study.

Genotype data will be transferred to the clinical database, and merged with the clinical data from the main study, prior to the statistical analysis and reporting of the study. Genotype data will (typically) be reported in the CSR for the main study.

12. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

12.1 Calculation or derivation of safety variable(s)

Patients will be considered evaluable for safety assessments, if they have received at least one dose of AZD7762.

The safety assessments will include CTCAE v. 3.0 grade and type of adverse events (AEs), changes in vital signs including blood pressure (BP), pulse, body temperature, changes in laboratory findings (including clinical chemistry, hematology, and urinalysis), cardiac markers (quantitative and qualitative troponinT), and changes in left ventricular ejection fraction (LVEF) by echocardiogram (ECHO)

All AEs will be classified by seriousness (serious or non-serious) and OAE will be identified as detailed in Section 7.3

12.1.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Drug Safety Physician, be considered OAEs and reported as such in the Clinical Study Report.

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

12.2 Calculation or derivation of efficacy variable(s)

12.2.1 Anti-tumor response activity

The exploratory objective to seek preliminary evidence of the anti-tumor activity of AZD7762 in combination with gemcitabine will be assessed in all patients with measurable disease by serial evaluations CT or MRI scans of tumor sites using RECIST criteria including overall tumor response rate, complete response (CR), partial response (PR), stable disease (SD). The investigator will evaluate tumor response in individual patients. Changes in non-measurable tumor will be noted.

12.3 Calculation or derivation of pharmacokinetic variables

The PK analyses will be performed by the Clinical PK/PD Group, Clinical Pharmacology, AstraZeneca Wilmington.

PK data from Cycle 0, Day 1 for each evaluable patient will be provided for each dose escalation meeting. The analysis will use nominal sample times. The results will be considered preliminary until the CSR is written.

PK analysis of AZD7762 and gemcitabine will be completed separately. Individual patient plasma concentration-time data will be analyzed by non-compartmental methods.

C_{max} for each patient will be assessed by visual inspection of the plasma concentration-time profile. C_{24h} will also be determined by visual inspection. If needed, the C_{24h} maybe extrapolated based on the results from compartmental or non-compartmental methods. The terminal elimination rate constant (λ_z) will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data (a minimum of 3 plasma concentration values in the terminal log-linear phase, spanning an interval of at least 2 half-lives). The $t_{1/2\lambda z}$ will be calculated as $0.693/\lambda_z$. area under the plasma concentration-time curve from zero to 48 hours ($AUC_{(0\text{-}48h)}$) and $AUC_{(0\text{-}t)}$ will be calculated by the linear trapezoidal rule. $AUC_{(0\text{-}t)}$ will be extrapolated to infinity using λ_z to obtain AUC where there are sufficient data (≤20% area extrapolated). CL will be calculated as Dose/AUC. MRT will be calculated as the ratio of area under the first moment curve (AUMC) to AUC plus the infusion duration divided by 2. V_{ss} will be determined by multiplying the CL by the MRT. Depending on the disposition of AZD7762, compartmental analysis of the AZD7762 plasma concentration time data may be utilized.

The following PK parameters of AZD7762 will be calculated based on the plasma concentration time profile obtained following a single dose on Cycle 0, Day 1 (AZD7762 alone) and Cycle 1, Day 8 (gemcitabine and AZD7762 combination): C_{max}, C_{24h}, AUC, $AUC_{(0\text{-}t)}$, CL, $t_{½\lambda z}$, MRT and V_{ss}.

The following PK parameters of gemcitabine will be calculated based on the plasma concentration time profile obtained following a single dose on Cycle 1, Day 1 (gemcitabine alone) and Cycle 1, Day 8 (gemcitabine and AZD7762 combination): C_{max}, AUC, $AUC_{(0\text{-}t)}$, CL, $t_{½\lambda z}$, MRT and V_{ss} (the "PK expansion group" only).

12.4 Calculation or derivation of pharmacodynamic variable(s)

Calculation or derivation of pharmacodynamic variable(s) are not applicable for this study.

12.4.1 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables (Not applicable)

12.4.2 Population analysis of pharmacokinetic/pharmacodynamic variables (Not applicable)

12.5 Calculation or derivation of pharmacogenetic variables

As the number of patients who will provide evaluable genetic data is unknown, no formal statistical modelling can be undertaken.

12.6 Calculation or derivation of health economics variables (Not applicable)

13. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

13.1 Description of analysis sets

Safety and tolerability data summaries will be based on all subjects who received at least one dose of study treatment.

DLT summaries will be based on all subjects who have completed Cycles 0 and 1 of treatment or experienced a DLT.

The summaries of antitumor activity, based on RECIST, will be based on all subjects with measurable disease at baseline (the most recent baseline RECIST assessment will be used).

The specific analysis sets for PK, PD, and genetic data will be defined in the statistical analysis plan (SAP), and will depend on the amount of missing data points.

Data from the patients who withdraw from the study, or who have missing values for other reasons, will be included in the analysis in such a way as to minimize any possible bias. This will be described in the SAP.

All patients will be included in the analysis according to the treatment received. A strategy for dealing with protocol deviations will be agreed by the investigators, Study Team Physician, pharmacokineticist and statistician as part of the SAP prior to database lock.

13.2 Methods of statistical analyses

There will be no formal statistical analysis in this study. All safety, tolerability and PK data will be summarized using descriptive statistics and exploratory graphical presentations of the data. Individual patient and geometric mean (by dose) plasma concentration plots will be

produced for gemcitabine and AZD7762, when administered as single agents or in combination. All summaries will be presented by dose, cycle and dosing schedule (ie, Schedule A or B [patients in the "PK expansion group" will be included in Schedule B]).

Descriptive statistics will be used for continuous (numeric) data, and counts and percentages will be used for categorical data summaries.

Additional exploratory analyses may be undertaken to better understand dose or concentration response relationship.

13.3 Determination of sample size

The primary objective of this study is to determine a safe dose of AZD7762 in combination with gemcitabine an ascending-dose tolerance study, hence the number of patients has been based on the desire to obtain adequate safety, tolerability and pharmacokinetic whilst exposing as few patients as possible to the study medication and procedures and as few patients as possible to doses that are unlikely to be effective modulators. In each dose level, 3-6 patients and 3 patients for the "PK expansion group" will be enrolled. Approximately 45 patients will be enrolled in this study.

The number of subjects that will agree to participate in the genetic research is unknown. A statistical analysis plan will be prepared where appropriate.

13.4 Timing of the analysis

13.4.1 Main analysis

The database for main analysis of the study will be locked after all registered patients have either withdrawn from study or completed Cycle 3. These data will be used for the statistical analysis and detailed in the CSR. The main conclusions on the primary, secondary, and exploratory objectives of this study will be made on the basis of these data.

13.4.2 Treatment completion analysis

The data collection may continue following the main analysis database lock (DBL), until all patients are off the study treatment. These data will provide supplementary information towards the primary objective of this study (to describe safety and tolerability of AZD7762) as well as the exploratory objectives. Any data not included in the main analysis DBL, will be reported as an addendum to the CSR.

13.5 Interim analyses (Not applicable)

No formal statistical interim analysis will be performed in this study.

13.6 Data and safety monitoring committee

The Data and Safety Monitoring Committee (DSMC) shall be managed according to the bylaws produced by AstraZeneca and the committee.

The DSMC will be established by AstraZeneca, but is independent from those directly involved in this study including AstraZeneca and the investigators.

The DSMC will appropriately assess at proper intervals the progress of this study and the safety data or other data, and recommend to AstraZeneca whether to continue, modify, suspend or discontinue the study on the basis of the safety or other information having been reported at the request by AstraZeneca. If the Dose Escalation Committee does not agree on the judgement of dose increase, the DSMC will provide advice.

The meetings of the DSMC will be held on an as-needed-basis at the request of AstraZeneca, the Dose Escalation Committee, and the members of the DSMC.

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