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Revised Clinical Study Protocol

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A Phase II Trial to Evaluate the Efficacy of AZD6094 (HMPL-504) in Patients with Papillary Renal Cell Carcinoma (PRCC)

Sponsor: AstraZeneca AB. 151 85 Sodertalje. Sweden

AstraZeneca Research and Development site representative

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

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

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PROTOCOL SYNOPSIS

A Phase II Trial to Evaluate the Efficacy of AZD6094 (HMPL-504) in Patients with Papillary Renal Cell Carcinoma (PRCC)

International Study Chair:

Study centre(s) and number of subjects planned

Approximately seventy-five subjects are planned to be enrolled at approximately 20 centres in North America and the European Union (EU).

Study period	Phase of development
Estimated date of first subject enrolled	Phase II
Estimated date of last subject completed	Phase II

Objectives

The primary objective of this study is to:

- Assess the anti-tumour activity of AZD6094 in patients with papillary renal cell carcinoma (PRCC) and in the subgroup of MET-positive patients as measured by investigator-assessment of overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. (Eisenhauer et al 2009).

The secondary objectives for this study are to:

- Assess the progression-free survival (PFS), change in target lesion tumour size from baseline, duration of response (DoR) and overall survival (OS) in patients with PRCC and in the subgroup of MET-positive patients according to RECIST v1.1.
- Assess the safety and tolerability of AZD6094 in the treatment of patients with PRCC.

- Characterise the pharmacokinetics (PK) of AZD6094 and the major metabolites M2 and M3 following administration to steady state after multiple dosing when given orally.
- Obtain a preliminary assessment of AZD6094 tumour activity by evaluation of pharmacodynamic (PDc) biomarker changes including total-cMet and phosphorylated-cMet.

The exploratory objectives for this study are to:

- Collect and correlate blood and tissue biomarkers with clinical endpoints e.g., germline/somatic mutations or aberrations related to AZD6094 pathways.
- Collect blood and urine from which metabolite analysis may be carried out.
- Investigate predictive markers of response and acquired resistance to AZD6094 in blood and tumour.
- Collect germline DNA blood samples for pharmacogenetic (PGx) analysis for future exploratory research into genes/genetic variation that may influence response (e.g., distribution, safety, tolerability and efficacy).
- Examine the relationship between the PK, PDc, safety, and efficacy markers.
- Collect patient reported outcomes (PRO) data to explore disease-related symptoms and health-related quality of life (HRQoL)
- To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility.

All exploratory analyses may be reported separately.

Primary Endpoint

- Objective tumour response (confirmed PR or CR) as assessed by RECIST v1.1.

Secondary Endpoints

- Week 12 and best percentage change from baseline in target lesion tumour size.
- Time-to-event endpoints: e.g., PFS, DoR and OS.
- PK parameters including AUC, C_{max}, T_{max}, Vz/F, CL/F, $t_{½}\lambda z$, and MRT.
- PDc assessments – total cMet-and phosphorylated-cMet.
- Safety and tolerability (as adverse events are characterised and graded by National Cancer Institute Common Terminology Criteria for Adverse Event [NCI CTCAE] v4.03).

Study design

This is an open-label, single-arm, multicentre, global, Phase II, study designed to evaluate the efficacy and safety of AZD6094 in patients with PRCC who are treatment naïve or previously treated.

An archival (or fresh if archival sample is not available) tumour sample is mandatory for this study. An independent central pathology review of tumour samples will be used to confirm the diagnosis of PRCC of all patients enrolling. However, locally available pathology results confirming PRCC will be allowed for timely study entry.

Screening and baseline assessments will be obtained within 28 days of first dose of AZD6094 as outlined in Table 3.

All patients entering the study will take AZD6094 600 mg by mouth (PO) once daily (QD). For the purposes of planning, a 3-week treatment period will be called a Cycle. Treatment will be given continuously.

Patients with easily accessible tumours should be asked to consent to the paired biopsy sampling portion of this study. Fresh biopsy pairs (pre-treatment and on-treatment [Cycle 1 Day 8]) will be collected to evaluate the PDc effect of AZD6094, which includes but is not limited to the analysis of phospho-cMet and total-cMet levels. The collection of fresh biopsies at tumour progression from patients with a previously confirmed objective tumour response is also encouraged in order to investigate the mechanisms of resistance. In addition, blood samples for PK, PDc, circulating tumour DNA (ctDNA), and PGx analysis will be collected from all consenting patients.

Following the baseline assessment, efficacy will be assessed by objective tumour assessments every 6 weeks (±7 days), for the first 12 months and every 12 weeks thereafter until objective disease progression as defined by RECIST v1.1.

Patients discontinuing treatment due to documented disease progression will enter a survival follow-up period, where they will be followed for the initiation of subsequent anti-cancer therapies every 3 months until death, loss to follow-up or withdrawal of consent, whichever comes first.

Patients discontinuing treatment prior to documented disease progression will enter a progression free survival follow-up period where they will continue to have disease assessments every 6 weeks for the first 12 months (of study drug) and then every 12 weeks thereafter until disease progression, death, loss to follow-up or withdrawal of consent, whichever comes first.

This study will comprise two stages. Stage 1 will include approximately 20 patients. If ≤ 2 tumour responses are observed in the first 20 evaluable patients, termination of the study will be considered taking into account the relevant molecular profile of the patients and additional information from related studies in the drug development programme. Since this is a non-binding futility analysis, there will be no saving of alpha (Type 1 error) for the end of the trial. If a decision is made to complete the trial, approximately 55 additional evaluable patients will be accrued in Stage 2 bringing the total number of evaluable patients to approximately 75.

An evaluable patient is defined as a one with centrally confirmed PRCC and with measurable disease at baseline who has received at least one dose of AZD6094.

Target patient population

Previously treated or untreated patients with locally advanced or metastatic PRCC are the target population for this study. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, in addition to adequate haematologic, liver and renal function. A pre-treatment archival tumour sample is mandatory for confirmation of PRCC pathology by a central laboratory. A fresh sample will be required if an archival sample is not available. Local pathology results will be utilised to enrol the patient.

Comparator, dosage and mode of administration

None.

Duration of treatment

Patients will receive continuous daily oral dosing of AZD6094 600 mg QD until RECIST v1.1 defined progression or until treatment discontinuation criteria is met (Section 5.9). There is no maximum duration of treatment duration as patients may continue to receive AZD6094 beyond RECIST v1.1 defined progression as long as they are continuing to show clinical benefit, as judged by the Investigator.

Outcome variable(s):

- Efficacy of AZD6094 as measured by the following variables:
  - Objective response rate assessed by RECIST v1.1
  - Week 12 and best percentage change from baseline in target lesion tumour size
  - Time-to-event endpoints: PFS, DoR and OS
- Pharmacokinetic parameters including AUC, C_{max}, T_{max}, Vz/F, CL/F, $t_{½}\lambda z$ and MRT
- Pharmacodynamics assessments – total-cMet and phosphorylated-cMet
- Safety and tolerability as measured by CTCAE v4.03

Statistical methods

In this Phase II, single-arm study of treatment naïve or previously treated PRCC patients, the anti-tumour activity of AZD6094 will be assessed. Descriptive statistics and graphic displays will be employed to assess the efficacy and safety of AZD6094, as well as hypothesis testing to assess efficacy at the end of the study. This study will comprise two stages. In Stage 1 approximately 20 patients will be enrolled. This group is considered sufficient to provide preliminary assessment of the anti-tumour activity of AZD6094 in the form of non-binding futility analysis. If ≤2 tumour responses are observed in the first 20 evaluable patients, termination of the study will be considered taking into account the relevant molecular profile of the patients and possibly additional information from related studies in the drug

development programme. Since this is a non-binding futility analysis, there will be no saving of alpha (Type 1 error) for the end of the trial. If a decision is made to complete the trial, approximately 55 additional evaluable patients will be accrued in Stage 2 bringing the total number of evaluable patients to approximately 75. .

An evaluable patient is defined as a one with centrally confirmed PRCC and with measurable disease at baseline who has received at least one dose of AZD6094.

At the end of the study the primary end-point (ORR) will be tested against the null H_0: ORR$\leq$25% at the one-sided significance level of α=0.025 in two populations as co-primary end points: the total population of confirmed PRCC patients and the subgroup of MET positive PRCC patients. Overall Family-wise Error Rate (FWER) will be controlled at the one-sided level α=0.025 using the Hochberg procedure.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACS	American Cancer Society
AE	Adverse event (see definition in Section 6.4.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Akt	protein kinase B
AST	Aspartate aminotransferase
BID	Twice daily
ctDNA	Circulating tumour DNA
CR	Complete response
CRF	Case Report Form
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P450
DAE	Discontinuation of Investigational Product due to Adverse Event
DBL	Database lock
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of Response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EGFR	Endothelial growth factor receptor
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
FACT-G	Functional Assessment of Cancer Therapy - General

Abbreviation or special term	Explanation
FISH	Fluorescence in situ hybridisation
FKSI-19	Functional Assessment of Cancer Therapy-Kidney Symptom Index-19
GCP	Good Clinical Practice
hERG	Human ether-a-go-go-related gene
HGF	hepatocyte growth factor
HIF-1α	hypoxia-inducible factor
HRQoL	Health-related quality of life
IATA	International Air Transport Association
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IFN-2	interferon-α
IHC	Immunohistochemistry
IL-2	interleukin-2
IP	Investigational Product
ITT	Intent-to-treat
LFT	Liver function test
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LVEF	Left Ventricular Ejection Fraction
MED	minimum efficacious dose
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal epithelial transition
MSKCC	Memorial Sloan Kettering Cancer Centre
mTOR	mammalian target of rapamycin
MUGA	Multi gated acquisition scan
NCI	National Cancer Institute
NGS	next generation sequencing
NOAELs	No observed adverse effect levels

Abbreviation or special term	Explanation
OAE	Other Significant Adverse Event (see definition in Section 11.2.3)
ORR	Overall response rate
OS	Overall Survival
PD	Progressive disease
PDc	Pharmacodynamics
PDGFβ	platelet-derived growth factor β
PFS	Progression free survival
PGx	Pharmacogenetic research
PI	Principal Investigator
PK	Pharmacokinetics
PO	By mouth
PR	Partial response
PRCC	Papillary renal cell carcinoma
PRO	Patient Reported Outcome
QD	Once daily
R_{AC}	Accumulation index
RCC	Renal cell carcinoma
RPTD	Recommended Phase II dose
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event (see definition in Section 6.4.2).
SC	Steering Committee
SCRI	Sarah Cannon Research Institute
SD	Stable Disease
TGFα	transforming growth factor α
TC	time course
TL	Target lesion
ULN	Upper limit normal
VEGF	vascular endothelial growth factor
VHL	von Hippel-Lindau
WBDC	Web Based Data Capture
WoCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

1.1.1 Renal cell carcinoma

Renal cell carcinoma (RCC) accounts for approximately 3% of all adult malignancies. In the United States, there are more than 65,000 new cases of RCC diagnosed each year and 13,500 RCC deaths annually (American Cancer Society). Worldwide, 270,000 new patients are diagnosed each year and up to 116,000 deaths occur due to RCC (Ljungberg et al 2011). RCC is more common in men than in women and it usually occurs between 50-70 years of age.

Renal cell carcinoma is a heterogeneous disease made up of several histological subtypes with different genetic and biochemical characteristics. Among the histologic variants of RCC, clear cell RCC is the most common, accounting for 75-90% of all renal malignancies. Papillary RCC (PRCC) is the most common of the non-clear cell renal carcinomas (10-15%), followed by chromophobe RCC (5%), and a group of rare subtypes (Bellmunt et al 2013).

Primary treatment of early stage RCC patients involves radical surgical resection curing more than 40-60% of patients, although many patients with localised disease will relapse (Linehan et al 2001). Approximately 25% of patients will present with locally advanced or metastatic disease at diagnosis. The prognosis for patients with distant metastases is poor, with a 5-year survival rate of 10% of patients with stage IV disease. Chemotherapy trials have shown RCC to be resistant to cytotoxic treatments (Motzer et al 2002) and cytokine-based treatment with interleukin-2 (IL-2) or interferon-α (IFN-α) provides benefit to only a small group of patients (Cohen et al 2005). Progress in understanding of underlying molecular biology of renal cell tumours has led to the development of effective therapeutic targets. Advances in RCC treatment have included anti-tumour agents that function as inhibitors of vascular endothelial growth factor (VEGF) angiogenesis and the mammalian target of rapamycin (mTOR). Approved agents targeting the VEGF pathway include, sunitinib, sorafenib, bevacizumab, pazopanib, and axitinib and for targeting the mTOR, temsirolimus, and everolimus.

1.1.2 PRCC and CMET pathway

Papillary RCC has been divided into type I and type II subtypes (Delahunt et al 1997). PRCCs occur in both sporadic and familial forms. Type I was described as having papillae covered by small cells with pale cytoplasm, small nuclei, foamy macrophages and psammoma bodies. Type II had papillae covered with large eosinophilic cells with large nuclei, prominent nucleoli, and psammoma bodies but uncommon foamy macrophages.

Type I hereditary PRCC, is an autosomal dominant disorder associated with multi-focal PRCC features. The causative gene, mutations in which are responsible for hereditary PRCC has been identified at chromosome 7 and encodes MET, a receptor tyrosine kinase (Cohen et al, 2005, Yang et al 2005). Mutations in the fumarate hydratase gene are observed in the familial subtype of type II PRCC which is associated with hereditary leiomyomatosis (Toro et al 2003).

A number of studies have shown that type II PRCC has a worse prognosis than type I PRCC based on univariate analysis but not always when multivariate analysis is performed (Logan 2013).

There is conflicting data regarding the prognostic importance of PRCC in comparison with clear cell cancer with some studies showing improved prognosis, others showing no difference and some showing an adverse prognostic effect (Logan 2013). However, conventional treatments for renal cell cancer appear to be less effective in patients with PRCC; following sunitinib therapy, the overall response rate (ORR) in patients, the majority of whom were previously untreated, is generally less than 10% and the median progression-free survival (PFS) ranges from 1.6-11.9 months, but is typically in the region of 6 months (Tannir et al 2012, Ravaud et al 2012, Molina et al 2012, Choueiri et al 2008, Lee et al 2012). This compares with a response rate of 25%-30% and median PFS of 9.5-11 months in sunitinib-treated patients with previously untreated clear cell cancer (Motzer et al 2002; Motzer et al 2002; Motzer et al 2007; Motzer et al 2013).

In a study of 92 patients with papillary renal cell cancer, 77% of which were confirmed centrally, first line everolimus was associated with a median PFS of 7.6 months (5.5-9.9) per local review and 3.7 months (2.3-5.5) per central review in the intent-to-treat (ITT) population (Escudier et al 2013). Median overall survival (OS) in the ITT population was 21.0 months (85% CI: 15.4-28.0). In a further study of 31 patients receiving first line everolimus the median PFS by investigator assessment was 5.1 months (Motzer et al 2013). In a study of 29 patients receiving either first line or subsequent line everolimus 2/29 (7%) had a partial response (PR), both of whom were treatment naïve (Koh et al 2013).

With better understanding of tumour biology, there is now evidence that the mesenchymal epithelial transition (MET) pathway in patients with PRCC is often activated thus driving disease progression.

cMet is a transmembrane receptor essential for embryonic development and wound healing normally activated through interaction with its specific ligand hepatocyte growth factor (HGF). Deregulation of cMet occurs in a wide range of human tumours, including such cancers as kidney, bladder, colorectal, lung, breast, ovarian, and pancreas. Activation of the cMet pathway triggers tumour growth, promotes tumour angiogenesis, and induces tumour metastases. Aberrant cMet activation in tumour can be achieved by four different ways: (a) with cMet gene amplification, (b) with HGF/cMet protein overexpression, (c) with cMet activating mutation and (d) with the formation of HGF/cMet autocrine loops. Mutations in the tyrosine kinase domain of cMet have been positively identified in patients with a hereditary form of PRCC, directly implicating cMet in human tumourigenesis (Schmidt et al 1997, Jeffers et al 1997). In addition, trisomy of chromosome 7 (residence of both cMet and its ligand HGF) is present in a high proportion of patients with PRCC, ranging from 45%-75% of patients (Choueiri et al 2013, Klatte et al 2009, Kovacs 1993, Fischer et al 1998).

Recently, a report of the oral multikinase inhibitor, Foretinib targeting MET, VEGF, RON, AXL and TIE-2 receptors demonstrated activity in a Phase II study of patients with PRCC. Choueiri et al studied 74 patients enrolled into two different dosing cohorts of 37 patients

each. Cohort stratification was based on MET pathway activation and the primary endpoint of the study was ORR. In Cohort A patients were dosed 240 mg once per day on days 1-5 every 14 days; in Cohort B 80 mg daily was administered. Sixty-seven patients were evaluable for response and mutation status. The ORR was 13.5% (95% CI, 6.7 to 23.5). The median duration of response (DoR) was 18.5 months, with a median duration of stable disease (SD) observed at 9.7 months. Of patients with germline mutation, 50% of 10 experienced a partial response (PR) and the remaining 50% with MET germline mutation had SD as best response. Adverse events (AEs) most frequently observed were hypertension, diarrhoea, and fatigue, with Grade 3 hypertension seen in 51% of patients. Eight patients experienced nine events of pulmonary emboli; none of these were fatal. Three patients were diagnosed with pulmonary emboli at the time of disease progression. Night blindness was reported in 8 patients. (Choueiri et al 2013).

A tumour response of 26 months duration was observed in a patient who received the cMet inhibitor PF-04217903 (Diamond et al 2013).

1.1.3 AZD6094 (HMPL-504)

AZD6094 is a potent and selective small molecule cMet kinase inhibitor, with IC_{50} of 3 to 5 nM for cMet kinase inhibition at enzyme and anti-tumour cell levels. Consistent with its potent enzyme and cell activity, AZD6094 was found to inhibit cell growth in vitro against tumours with cMet amplification in the absence of HGF-stimulation with IC_{50}s generally below 10 nM. It also potently inhibited HGF-stimulated cell proliferation against tumours with cMet overexpression or carrying a HGF/cMet autocrine loop. In human xenograft mice models, AZD6094 demonstrated excellent anti-tumour activity against cMet gene amplified gastric and lung tumours following once daily treatment. In tumours with both cMet and epidermal growth factor receptor (EGFR) overexpression, it was found that combination of AZD6094 with erlotinib, an EGFR inhibitor, was more effective than either agent alone (AZD6094 Investigator's Brochure [IB]).

1.1.4 Non-clinical information and correlative studies

Summary of *in vitro* activity

The *in vitro* study results have shown that AZD6094 is a reversible ATP-competitive cMet inhibitor with high selectivity over 274 kinases. It potently inhibits cMet phosphorylation and cell functions related to cMet phosphorylation such as HGF dependent or independent tumour cell proliferation. It was found that AZD6094 had a potent inhibitory effect on tumour cell survival against tumours with constitutive cMet activation (phosphorylation) due to cMet gene amplification or with a HGF/cMet autocrine, suggesting that patients with these genotypes will be most likely to respond to AZD6094 treatment. The tumour cells with high cMet expression also responded to AZD6094, but in a ligand-dependent manner, suggesting that the patients with high levels of cMet and HGF might benefit from cMet therapy. Finally, when independent activation of other targets is present, combination therapy may provide more optimal effect by simultaneous suppression of the different targets.

Three metabolites of AZD6094 were identified and synthesised. The *in vitro* activity of these metabolites on inhibiting cMet kinase was evaluated. Results show that only M2 (HM5018454) demonstrates potent inhibitory activity on cMet kinase with an IC_{50} of 0.006 μM. Other metabolites, M3, and M4, demonstrated little activity against cMet kinase with an IC_{50}>1μM. M2 also demonstrated activity against autophosphorylation of cMet in NCI-H441 cells with an IC_{50} of 0.011μM. M2 showed good activity against cell survival and proliferation in cMet gene amplified cell lines, including MKN-45, Hs746T, and EBC-1 with either IC_{50}: 0.024, 0.015 and 0.016 μM or GI_{50}: 0.019, 0.011 and 0.013 μM, respectively. Consistent with growth inhibition, M2 inhibited activation of cMet and its downstream signal molecules, such as protein kinase B (Akt) and ERK in cMet gene amplified cell line Hs746T in a dose-dependent manner.

Refer to the AZD6094 IB for additional information.

Summary of *in vivo* activity

The inhibition of cMet phosphorylation in the tumour tissue *in vivo* by AZD6094 was studied in NCI-H441 xenograft. AZD6094 was found to inhibit cMet phosphorylation in the tumour in a dose- and time-dependent manner. Following a single dose of AZD6094 in NCI-H441 subcutaneous xenograft mice, the ED_{50} for the inhibition of cMet phosphorylation was 1 mg/kg with a corresponding EC_{50} in plasma and tumour of 5.4 ng/mL and 28.4 ng/g, respectively. In the time course (TC) study, after animals were given a 5 mg/kg dose of AZD6094, ≥90% inhibition of cMet phosphorylation was maintained for at least 8 hours with plasma and tumour drug concentrations of 27.5 ng/mL and 63.5 ng/g respectively at the 8 hour time point in the NCI-H441 tumour. A similar observation was found in cMet gene amplified human gastric cancer Hs 746T xenograft model. AZD6094 was found to inhibit cMet phosphorylation in a dose- and time-dependent manner, and correlated well with the drug concentration in plasma and tumours, the ED_{50} was about 0.6 mg/kg at 4 hours, and corresponding EC_{50} in plasma was about 3.6 ng/mL.

The anti-tumour activity of AZD6094 was evaluated in several tumour models in mice. It was found that AZD6094 was highly effective in tumours where cMet activation drives tumour growth, such as gastric cancer with cMet gene amplification. The minimum efficacious dose (MED, defined as ≥58% tumour growth inhibition) in these models ranged from 1.0 to 2.5 mg/kg once daily. Secondly, in tumours where both cMet and EGFR are overexpressed, it was found that the combination of AZD6094 and erlotinib provided synergistic activity. Finally, AZD6094 was found effective against glioblastoma tumours carrying an HGF/cMet autocrine loop either in subcutaneous or brain orthotopic models. In all these models a good dose response of AZD6094 was observed. There appears generally to be a good correlation between inhibition of cMet phosphorylation in the tumour and inhibition of the tumour growth.

The metabolite of AZD6094, M2 (HM5018454) was found to have potent cMet inhibitory activity both in vitro and in vivo. In cMet gene amplified human gastric cancer Hs 746T xenograft model, M2 suppressed cMet phosphorylation in a dose- and exposure-dependent manner, the ED_{50} at 4 hours was about 1.4 mg/kg, and EC_{50} in plasma was about 14.3 ng/mL

after a single oral dose of M2. Compared to the parent drug, M2 was less potent by 3-4 fold. The dose dependent anti-tumour activity of M2 was shown in the subcutaneous Hs746T model, after M2, 3 mg/kg once a day, was orally administered to nude mice for two weeks. The latter dose induced TGI by 83%; M2 at 10 and 30 mg/kg regress the tumour by 60% and 95%, respectively. The TGI of M2 at 3 mg/kg was similar to that of parent drug AZD6094 at 1 mg/kg (TGI=84%), suggesting M2 was 3 fold less potent than the parent drug. Furthermore, plasma area under the curve (AUCs) of M2 was 20% of parent drug after dosing with AZD6094, indicating M2 contributed minimally to anti-tumour effect of AZD6094 in nude mice; however the M2 exposures in other species should be noted.

In summary, AZD6094 is a potent and selective small molecule cMet kinase inhibitor. It was found to possess significant anti-tumour activity as a single agent against tumours with constitutive cMet activation, such as cMet gene amplification or HGF/cMet autocrine loop. In tumours with activation of multiple pathways, combination therapy may be more effective than the single agent. The effect of AZD6094 on tumours with cMet overexpression, such as oesophageal, lung and colon where cMet activation and tumour growth depend on the stimulation by HGF, are worth exploring further.

Refer to the AZD6094 IB for additional information.

Non-clinical safety studies

The non-clinical safety of AZD6094 has been evaluated in general toxicology studies of up to 3 months duration in rats and dogs, an embryofoetal study in rats, and also in safety pharmacology and genetic toxicology studies and an in vitro phototoxicity test.

In repeat dose toxicology studies of up to 13 weeks in duration in rats and dogs, the principal target organs/tissues for toxicity were gastrointestinal tract (degenerative changes) and lymphoreticular system, including lymph nodes, thymus, spleen, and Peyer's patches (decreased cellularity).

After dosing for 1 month, in addition to GI and lymphoreticular effects, there were findings in heart (isolated instances of low grade myocardial degeneration), liver (hepatocellular hypertrophy), thyroid (follicular hypertrophy), adrenals (cortical hypertrophy), eyes (hyperaemia in the conjunctiva in dogs), prostate and female reproductive tract (atrophy/degenerative changes). All toxicities had recovered 28 days after cessation of dosing with the exception of eye changes in dogs, and stomach epithelial hyperplasia, hepatocyte hypertrophy and thyroid follicular cell hypertrophy in rats.

Reversible effects in liver, thyroid, adrenals and female reproductive tract were seen after 13 weeks, and additionally, there were some reversible changes in bladder and kidney in rats (epithelial hyperplasia) and testes in dogs (dysgenesis).

In rats there was evidence of reproductive toxicity including adverse effects (AEs) on embryofoetal survival and development.

In safety pharmacology studies, there was no evidence of effects on cardiovascular, respiratory or neurobehavioural parameters.

There is no evidence of genotoxicity in vitro/in vivo studies conducted to date. Results of an in vitro (3T3) test may suggest potential for phototoxicity. Refer to the AZD6094 IB for additional information.

1.1.4.1 Non-clinical pharmacokinetics

The pharmacokinetic (PK) properties of AZD6094 were investigated with *in vitro* and *in vivo* assays. AZD6094 was rapidly absorbed following oral administration with an average of $T_{½}$ ranging between 2 and 7 hours in mouse, rat and dog. The bioavailability was moderate to high in mouse, rat, and dog, but poor in monkey due to extensive metabolism mediated by aldehyde oxidase. The protein binding was moderate, ranging from 40 to 80% in different species. Tissue distribution was low to moderate with minimal potential for significant drug accumulation. Clearance was moderate in mouse, rat and dog, high in monkey and predicted to be low in humans. AZD6094 can be metabolised by multiple enzymes in humans.

AZD6094 had a weak inhibitory effect on cytochrome P450 (CYP) 2C8 in vitro, with no CYP induction identified. AZD6094 is not a substrate of P-glycoprotein (Pgp) however it is a weak inhibitor in vitro. The excretion of AZD6094 after oral administration been fully characterised in rats, which indicated approximately 30% of radioactivity was excreted in urine and 66% in faeces. Overall, AZD6094 has demonstrated favourable PK properties for oral administration and was predicted to have rapid oral absorption with good oral bioavailability, low to moderate clearance and tissue distribution, low risk of drug accumulation and drug-drug interaction (DDI).

Refer to the AZD6094 IB for additional information.

1.1.5 Clinical information

1.1.5.1 Safety and efficacy in humans

AZD6094 has been evaluated in several clinical studies, including both Phase I and Phase II studies in a variety of combinations and tumour settings. AZD6094 has been administered at various doses ranging from 100 mg to 1000 mg per day. A Phase I dose escalation study in patients with advanced cancer in Australia (D5081C00001 – NCT01773018) determined the maximum tolerated dose (MTD) to be 800 mg once daily (QD).

The most commonly reported AEs (occurring in ≥10% of patients overall) irrespective of causality reported include: nausea, vomiting, fatigue, constipation, oedema peripheral and dizziness, decreased appetite, and headache and diarrhoea. The AEs reported that were CTCAE Grade 3 or higher include fatigue, deep vein thrombosis, ALT increased, blood ALP increased and hyperglycaemia. SAEs reported in more than 1 patient include: pyrexia, and deep vein thrombosis, fatigue and febrile neutropenia.

The two patients that had AEs that resulted in death include: one patient that died due to cancer progression (recorded as non-treatment related by the investigator) and one patient that

had an SAE of hepatic encephalopathy that resulted in death (considered by the investigator to be related to AZD6094).

The AEs of nausea, vomiting, oedema peripheral, fatigue and elevations of liver enzymes and DILI are considered as expected events (identified risks) for AZD6094 treatment.

Limited data for efficacy are available at the current time. In Study D5081C00001, 2 patients diagnosed with PRCC in the 600 mg QD cohort (1 patient received treatment for 1 year; 1 patient is ongoing treatment at 19 months) and 1 patient diagnosed with PRCC in the 1000 mg QD cohort (patient is ongoing treatment at 13 months) have achieved a partial response. In addition, another patient with PRCC in the 300 mg twice daily (BID) cohort achieved a 27% tumour reduction at Cycle 5. In a Phase I dose escalation study in patients with advanced cancer in China (D5081C00002 - NCT01985555), 1 patient with advanced gastric cancer has had a 28% tumour reduction following treatment with AZD6094.

Refer to the AZD6094 IB for additional information.

1.1.5.2 Pharmacokinetics

Preliminary pharmacokinetic (PK) data are included from Study D5081C00001. Preliminary single and multiple dose PK data are available following dosing with 100mg, 200mg, 400mg, 600mg and 800mg. Following administration of single doses, exposure was typified by absorption with a T_{max} of approximately 1.0-2.7 hours followed by an elimination phase. The terminal half-life ($t_{1/2}$) ranged from 3.6-6.8 hours, consistent with achieving steady state by Day 3 of treatment. The dose-normalized exposure (C_{max} and AUC) of AZD6094 after single doses, indicated that exposure may not be dose-proportional over the range of 100 to 800 mg but the moderate variability observed may have influenced this conclusion. The oral clearance (CL/F) ranged from 27-48 L/h and volume of distribution (Vz/F) ranged from 219-322 L.

Following multiple doses, T_{max} occurred at a range of 1.3-2.7 hours, which is similar to that observed after a single dose followed by elimination which was generally consistent with the early elimination after single doses. There appeared to be no trend for accumulation of AZD6094; R_{AC} values were approximately 1, and consistent with a relatively short $t_{1/2}$. Overall the multiple dose PK was consistent with the single dose data. The AUC_{ss} exposure on Day 21 indicated that exposure may not be dose-proportional over the range of 100 to 800 mg but the moderate variability observed may have influenced this conclusion.

The main metabolites M2 and M3 were rapidly formed following oral administration of the parent drug resulting in a Tmax range from 1.2-3.8hr. The relationship between dose and Cmax and AUC displayed nonlinear traits, which was supportive of observations made with the parent compound. Plasma profiles after multiple dosing were similar for each individual after single and multiple dosing, such that subjects with low M2 or M3 levels on day 1 also showed low levels at steady state. The mean $T_{1/2}$ for M2 and M3 was in a similar range and was variable within cohorts, ranging from 5.5 –16.1hr.

1.2 Research hypothesis

The research hypothesis is that AZD6094 monotherapy will demonstrate anti-tumour activity as measured by ORR, duration of objective response, tumour size analysis, PFS and OS, and will have an acceptable safety profile when administered to PRCC patients.

1.3 Rationale for AZD6094 in PRCC

This is a Phase II study of AZD6094 in patients with advanced or metastatic PRCC, presenting with or without previous treatment. This trial is justified for the following reasons:

- The relevance of altered cMet signalling in RCC and in particular in PRCC has been established. For PRCC, germline and somatic mutations in the tyrosine kinase domain of cMet have been identified and shown to drive the disease. In addition, trisomy of chromosome 7 is present in approximately 45-75% of patients with PRCC. Several preclinical studies have shown that cMet signalling was found to be an alternative pathway for angiogenesis and may play a role in adaptive resistance to VEGF blockade.

- AZD6094 is capable of inhibiting tumour growth in vivo when applied as monotherapy in models in multiple indications harbouring MET aberrations, and has already shown preliminary clinical efficacy in patients with PRCC in an ongoing Phase I study.

- AZD6094 has been administered to patients with advanced cancer in ongoing Phase I studies investigating the appropriate dose level for this Phase II study. Based on preliminary data from these studies the administration of AZD6094 was generally well tolerated with the majority of events being of low grade and with a low incidence of treatment-related withdrawals.

Further details on the study and statistical design are provided in Sections 11 and 12.

1.4 Benefit/risk and ethical assessment

1.4.1 Potential for benefit

Patients with advanced or metastatic PRCC have no curative or standard of care treatment options. Standard therapies used to manage patients with renal cell cancer appear to be less effective in patients with PRCC compared to those with clear cell cancer. Aberrant cMet activation is prominent in PRCC tumours as a result of cMet gene amplification, HGF/cMet protein overexpression, cMet activating mutation or HGF/cMet autocrine loops. Mutations in the tyrosine kinase domain of cMet have been positively identified in patients with a hereditary form of PRCC, (type 1) directly implicating cMet in human tumourigenesis. In addition, trisomy of chromosome 7 (residence of both cMet and its ligand HGF) is present in 45%- 75% of patients with PRCC. Foretinib, an inhibitor of cMet and VEGFR2 has shown activity in patients with PRCC with a response rate of 13.5% of 74 patients and median progression of 9.3 months (95% CI, 6.9 to 12.9 months).

Limited data for efficacy are available at the current time. In Study D5081C00001, 2 patients diagnosed with PRCC in the 600 mg QD cohort (1 patient received treatment for 1 year; 1 patient is ongoing treatment at 19 months) and 1 patient diagnosed with PRCC in the 1000 mg QD cohort (patient is ongoing treatment at 13 months) have achieved a partial response. In addition, another patient with PRCC in the 300 mg BID cohort achieved a 27% tumour reduction at Cycle 5. In a Phase I dose escalation study in patients with advanced cancer in China (D5081C00002 - NCT01985555), 1 patient with advanced gastric cancer has had a 28% tumour reduction following treatment with AZD6094.

Refer to the AZD6094 IB for additional information.

1.4.2 Risk minimisation activities for potential risks associated with AZD6094

The following section highlights risk minimisation activities for the key potential risks identified in either preclinical studies or from ongoing clinical studies.

Diarrhoea

Diarrhoea has been observed in some patients receiving AZD6094. There are no standard exclusion criteria for patients with diarrhoea; however, patients with previous gastrointestinal surgery that may affect drug absorption are excluded from AZD6094 clinical studies. Diarrhoea can be managed with anti-diarrhoeal treatment and interruptions to AZD6094 dosing. Patient reports of diarrhoea are expected to be evaluated and treated by investigators according to local practice (e.g., use of medications such as loperamide, need for intravenous [IV] fluid replacement).

Nausea and Vomiting

Nausea and vomiting has been observed in the study D5081C00001 and appears to be dose related. The majority of events are Grade 1. Patients with uncontrolled nausea and vomiting will be excluded from this study. Patient reports of nausea and vomiting are expected to be evaluated and treated by investigators according to local practice (e.g. use of anti-emetic therapy, need for IV fluid replacement).

Fatigue

Fatigue has been reported in study D5081C00001 patients receiving AZD6094, the majority of which were considered to be related to the drug. The events were either Grade 1 or 2 with the exception of one patient receiving AZD6094 800mg who had Grade 3 fatigue which was considered to be a DLT. Patients entering study D5082C00002 will be restricted to performance status 0 or 1. Fatigue will be monitored by standard adverse event reporting.

Liver Function Tests

Abnormal LFTs were reported in three patients receiving AZD6094 in study D5081C00001, with one of the events being considered a DLT. Patients with significantly abnormal liver function tests will be excluded from study D5082C00002. Liver function will be carefully monitored by frequent measurement of transaminases and bilirubin in blood.

Hepatic Encephalopathy

A fatal event of hepatic encephalopathy was reported in one patient receiving AZD6094 (600 mg) in study D5082C00002. The investigator considered that there was a causal relationship between death due to hepatic encephalopathy and AZD6094.

The majority of tyrosine kinase inhibitors approved by regulatory agencies are reported to induce hepatic injury, usually detected in the first few cycles of treatment (Shah et al 2013). Hence this revised edition of the protocol includes more frequent monitoring of liver function tests during the clinical study, with the institution of weekly monitoring of liver function tests until the end of Cycle 3 (or 9 weeks whichever is sooner) and continued monitoring beyond Cycle 3 as described in Table 3. In addition, investigators should review the patient's current concomitant medications, and assess the need for the patient to continue on hepatic metabolism modifying agents, such as statins.

Phototoxicity and/or Rash

Results of an in vitro (3T3) test may suggest potential for phototoxicity. Measures to prevent photosensitivity have been included in ongoing studies of AZD6094. There have been no reported cases of photosensitive rash. Adverse events of Grade 1 rash, erythema and pruritus have been reported in some patients. During AZD6094 therapy and for 4 weeks after the last dose patients should be advised to avoid prolonged exposure to sun, wear protective clothing and a hat and seek shade from the sun as far as possible; in addition an SP30+ sunscreen should be used. Exposure to other sources of UV light including sunbeds, tanning booths, etc. should be avoided. If sunburn occurs, it is important to discontinue the study drug and take action under the direction of a doctor. Keeping the area of skin eruption moist and applying wet dressings may help relieve the symptoms. Reactions may last a few days, however severe reactions may last up to a few weeks. Topical steroid creams may be helpful in treating the redness, and antihistamines are generally helpful in minimizing the itching. In severe cases, a short course (10-14 days) of oral steroids, under the direction of a doctor, can be used.

Renal Function

Renal toxicity has been observed another cMet inhibitor, SGX523, thought to be due to an insoluble metabolite causing crystal nephropathy (Infante et al 2013).

Grade 2 blood creatinine increase was observed in one patient receiving AZD6094 600 mg, and at the time of data cut off was reported as ongoing. Grade 1 blood creatinine increase was observed in one patient receiving AZD6094 800mg daily, which resolved. Both events were considered by the investigators to be possibly related to AZD6094 daily.

There is no information from ongoing AZD6094 clinical studies regarding levels of parent drug and metabolites in urine. However in a study of rats, excretion of AZD6094 was very low (<0.5%) and urinary excretion of metabolites was the primary route of excretion, in particular M2, which accounted for approximately 11% of the dose. In a study of radiolabelled AZD6094, in which rats underwent biliary cannulation, up to 42% of the

radiolabel was excreted via urine suggesting that many of the metabolites formed are excreted via the urine in rats.

Urine samples will be collected in this study for assessment of parent and the major metabolites M2 and M3. However, based on the structure of AZD6094 and its metabolism it is not anticipated that a metabolite-induced crystal nephropathy will be associated with administration of AZD6094.

It is anticipated that the majority of patients entering this trial will have had a prior nephrectomy. Patients with a Glomerular Filtration Rate (GFR) <40 mL/min, as assessed using the standard methodology at the investigating centre (e.g. Cockcroft-Gault, MDRD, or CKD-EPI formulae, EDTA clearance or 24-hour urine collection) will be excluded.

Renal function will be carefully monitored by frequent measurement of blood urea, creatinine and electrolytes.

Oedema

Oedema has been observed in some patients receiving AZD6094. These events have been Grade 1 or 2, and the incidence does not appear to be dose related. Oedema has also been observed with other cMet inhibitors including onartuzumab and crizotinib. Oedema should be monitored by clinical examination and measurement of weight. Diuretic therapy should be considered at the discretion of the Investigator. Renal function will be carefully monitored.

Drug-drug interaction

Whilst the overall risk of drug-drug interactions with AZD6094 is low, caution should be exercised when coadministering AZD6094 with other drugs as described below. AZD6094 showed no induction effects on human CYP450 enzymes in the human liver cell experiment. In addition AZD6094 showed no significant competitive inhibition of the major subtypes of human CYP450 enzyme and no time-dependent inhibition, with the exception of weak competitive inhibition of CYP2C8 (IC50=9.1μM). Those drugs defined as strong 2C8 substrates (almost exclusively metabolized by 2C8, such as Repaglinide and Rosiglitazone) should be used with caution. AZD6094 is not a substrate of Pgp but is a weak inhibitor in vitro (IC50 17.9 μM). Drugs that are known to be affected by Pgp such as digoxin, quinidine, loperamide, saquinavir and ritonavir should be used with caution. Based upon studies of in vitro liver microsomes and S9 fractions AZD6094 is metabolized by several metabolic enzymes, including both CYP450 enzymes and some NADPH-independent non-CYP enzymes. Appendix I provides a list of strong inhibitors and strong inducers of CYP3A4, strong inhibitors of CYP1A2, CYP3A4 substrates which have a narrow therapeutic range and CYP3A4 sensitive substrates. Patients receiving strong inhibitors or strong inducers of CYP3A4, strong inhibitors of CYP1A2, or CYP3A4 substrates which have a narrow therapeutic range within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort) will be excluded.

Concomitant use of drugs that are known to be strong inducers of CYP3A4, strong inhibitors of CYP3A4 or CYP1A2, CYP3A4 substrates which have a narrow therapeutic range or

CYP3A4 sensitive substrates during the trial should be avoided as far as possible unless considered essential by the investigator, in which case patients must be monitored closely for potentially reduced efficacy or increased toxicity due to drug-drug interactions (Appendix I).

Testicular toxicity

In the 13-week dog study, testicular dysgenesis with no mature sperm in the epididymis was noted. The effect was not apparent after a 4-week recovery period. As younger animals were used, this finding may be related to sexual immaturity in these dogs, rather than being a direct effect of the compound. The exposure level at the no observed effect level (NOEL) may be similar to the exposure level in some patients at 600 mg/day.

Male patients must use a condom during sexual intercourse with all sexual partners including a pregnant female partner during the study and for 4 weeks after discontinuing study treatment. However, where a sexual partner of a male participant is a woman of childbearing potential who is not using effective contraception, men must use a condom during sexual intercourse during the study and for 6 months after discontinuing study treatment.

Male patients should avoid procreation during the trial and for 6 months after discontinuing study treatment.

Male patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment.

1.4.3 Overall risk/benefit assessment

The investigation or AZD6094 in this patient population appears acceptable based upon the non-clinical safety profile, the emerging clinical safety profile, the risk minimisation and adverse event management proposals, early evidence of activity in patients with PRCC, the lack of effective alternative treatments and the strength of the scientific hypothesis under evaluation. Overall the benefit/risk assessment supports the administration of AZD6094 to patients with PRCC in accordance with this protocol.

1.4.4 Steering committee

A Steering Committee (SC) will be formed of multidisciplinary members selected by AstraZeneca and LLC (for this 2-stage study. Details will be outlined in the Steering Committee Charter. The SC is composed of experts who provide clinical and methodological expertise as it relates to the development of AZD6094 in renal cancer and includes representatives from AstraZeneca and The SC expertise will be used to provide feedback to the Sponsor on the activity of AZD6094 based upon a review of data from patients in Stage 1 of the study.

The SC may convene on an ad hoc basis in the event that a safety signal is identified.

SC members may also use their expertise and experience to provide the following services in support of the D5082C00002 trial:

- Ongoing input into the scientific conduct of the trial.
- Ongoing consultation or advice on issues related to study safety or study recruitment.
- Consultation to the Sponsor on study-related issues that may require a protocol amendment.
- Present approved study information to investigators, study staff and/or the oncology community at in-person or web/teleconference study-related meetings.
- Identification and evaluation of trial barrier due to accrual, feasibility, clinical implementation or logistical issues.
- Review comparator or competing trial information/SOC/NCCN guidelines and FDA guidance.

Any outcome of these reviews affecting safety or study design will be communicated in a timely manner to the participating investigators by so that they may notify their Institutional Review Boards/Ethics Committees (IRBs/ECs).

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to:

- Assess the anti-tumour activity of AZD6094 in patients with PRCC and in the subgroup of MET-positive patients as measured by investigator-assessment of ORR according to RECIST v1.1.

2.2 Secondary objectives

The secondary objectives for this study are to:

- Assess the progression-free survival (PFS), change in target lesion tumour size from baseline, duration of response (DoR) and overall survival (OS) in patients with PRCC and in the subgroup of MET-positive patients according to RECIST v1.1.
- Assess the safety and tolerability of AZD6094 in the treatment of patients with PRCC.
- Characterise the pharmacokinetics (PK) of AZD6094 and the major metabolites M2 and M3 following administration to steady state after multiple dosing when given orally.

- Obtain a preliminary assessment of AZD6094 activity tumour by evaluation of PDc biomarker changes including, total-cMet and phosphorylated-cMet.

2.3 Exploratory objectives

The exploratory objectives for this study are to:

- Collect and correlate blood and tissue biomarkers with clinical endpoints e.g., germline/somatic mutations or aberrations related to AZD6094 pathways.
- Collect blood and urine from which metabolite analysis may be carried out.
- Investigate predictive markers of response and acquired resistance to AZD6094 in blood and tumour.
- Collect germline DNA blood samples for pharmacogenetic (PGx) analysis for future exploratory research into genes/genetic variation that may influence response (e.g., distribution, safety, tolerability and efficacy).
- Examine the relationship between the PK, PDc, safety, and efficacy markers.
- Collect patient reported outcomes (PRO) data to explore disease-related symptoms and health-related quality of life (HRQoL).
- To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility.

All of these exploratory analyses may be reported separately.

2.4 Endpoints

2.4.1 Primary Endpoint

- Objective tumour response (confirmed PR or CR) as assessed by RECIST v1.1.

2.4.2 Secondary Endpoint

- Week 12 and best percentage change from baseline in target lesion tumour size.
- Time-to-event endpoints: e.g., PFS, DoR and OS.
- PK parameters including AUC, C_{max}, T_{max}, Vz/F, CL/F, $t_{½}\lambda z$ and MRT.
- PDc assessments – total-cMet and phosphorylated-cMet.
- Safety and tolerability (as adverse event are characterised and graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03).

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design

This is an open-label, single-arm, multicentre, global, Phase II, 2-staged study designed for patients with locally advanced or metastatic PRCC. All enrolling patients must provide a pre-treatment tumour sample (archival or fresh) for confirmation of PRCC. An independent central pathology review will be utilised to confirm the PRCC histology of all patients. Local confirmation of PRCC will be allowed for study entry.

For the purposes of planning, a 3-week treatment period will be called a Cycle. AZD6094 600 mg PO QD will be administered continuously every 3 weeks until RECIST v1.1 defined progression or until treatment discontinuation criteria is met (Section 5.9). Patients may continue to receive AZD6094 beyond RECIST v1.1 defined progression as long as they are continuing to show clinical benefit, as judged by the Investigator.

Patients will undergo restaging for anti-tumour activity of AZD6094 every 6 weeks (±7 days) as detailed in the study plan (Table 3). If AZD6094 is discontinued for reasons other than disease progression, the patient must continue RECIST v1.1 assessments every 6 weeks until disease progression, even if further lines of anticancer therapy are administered.

Patients should be asked to consent to the paired biopsy sampling portion of this study. Fresh biopsy pairs (pre-treatment and on-treatment Cycle 1 Day 8) will be collected to evaluate the PDc effect of AZD6094, which includes but is not limited to phospho-cMet and total-cMet levels. The collection of fresh biopsies at tumour progression from patients with a previously confirmed objective tumour response is also encouraged in order to investigate the mechanism of drug resistance. Blood samples for PK, PDc, ctDNA, and PGx analysis will be collected from all patients in this study.

Should safety or efficacy signals emerge from this group of patients, the protocol may be modified or discontinued. Alternative dosing schedules e.g. continuous twice daily dosing, and/or changes in dose may be instigated in response to emerging safety, tolerability, or PK data from this study and additional ongoing studies.

In addition, any outcome of the SC review pertinent to the continued conduct of the study will be communicated in a timely manner to the participating investigators by so that they may notify their IRBs/ECs.

3.2 Rationale for study design, doses and translational research

Rationale for study design and doses

The study will comprise two stages. In Stage 1 approximately 20 patients will be enrolled. This group is considered sufficient to provide preliminary assessment of the anti-tumour activity of AZD6094 in the form of non-binding futility analysis.

If ≤2 tumour responses are observed in the first 20 evaluable patients termination of the study will be considered taking into account the relevant molecular profile of the patients and additional information from related studies in the drug development programme. Since this is a non-binding futility analysis, there will be no saving of alpha (Type 1 error) for the end of the trial. If a decision is made to complete the trial, approximately 55 additional evaluable patients will be accrued in Stage 2 bringing the total number of evaluable patients to approximately 75. The total number of approximately 75 evaluable patients is considered sufficient to provide a robust assessment of the level of efficacy associated with AZD6094 and to characterise the safety and tolerability of AZD6094 in patients with PRCC.

At the end of the study the primary end-point (ORR) will be tested against the null H_0: ORR≤25% at the one-sided significance level of α=0.025 in two populations as co-primary objectives: in the total population of confirmed PRCC patients and the subgroup of MET positive PRCC patients. Overall Family-wise Error Rate (FWER) will be controlled at the one-sided level α=0.025 using the Hochberg procedure. Based on current assumptions about the prevalence of MET-positive subpopulation in PRCC patients and about response rates to the drug, 75 patients would provide greater than 90% power to reject the null in at least one of the study populations (the total population and the subgroup).

The dose of AZD6094 600 mg QD has been selected based upon data from the ongoing Phase I studies. In study D5081C00001, as of confirmed partial responses were observed in both of the PRCC patients receiving AZD6094 600mg QD, but in neither of the two patients receiving 800mg QD. A lower dose level than 600mg QD may be effective but no patients with PRCC have received doses lower than 600mg QD to support this hypothesis.

AZD6094 600mg QD has been generally well tolerated. At this dose level AEs included but were not limited to nausea, vomiting, diarrhoea, constipation, fatigue, and oedema. These were typically Grade 1 and Grade 2; one patient reported DLTs of febrile illness and abnormal LFTs. Ongoing dosing of 600mg QD in 2 PRCC responder patients for 27 weeks and 34 weeks respectively supports the selection of 600mg QD as a tolerable dose suitable for evaluation in this study. Adverse events will be managed with supportive medication and where necessary dose adjustments or treatment delays are recommended as per Section 5.5.

Rationale for exploratory analysis

In vivo preclinical models harbouring cMet alterations (over-expression, amplification, mutation, copy number gain) have been shown to be sensitive to AZD6094, suggesting a potentially useful positive predictive value for cMet alterations.

Patients will be required to provide archival tumour samples (fresh tumour sample pre-dose if archival is not available) in this study, to (a) confirm papillary histology, and (b) characterise tumour molecular and protein expression alterations. An additional tumour biopsy on progression is also requested from consenting patients who have achieved a confirmed objective tumour response, and will be used to study mechanisms of AZD6094 resistance and possible combination opportunities for the future. In addition, blood samples for PK, PDc, and PGx analysis will be collected. Collection of fresh pairs of tumour sample from patients (pre-dose and on-treatment) is encouraged to confirm pathway inhibition by analysis of relevant biomarkers. In addition, blood samples for PK, PDc, ctDNA, and PGx analysis will be collected from consenting patients.

AstraZeneca may perform genetic research in the AZD6094 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD6094. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD6094, but also susceptibility to cancer for which AZD6094 may be evaluated. Thus, this genetic research may involve the study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

Future exploratory analyses will be guided by emerging data from this and other studies with AZD6094. The results of this exploratory research will not necessarily form part of the clinical study report (CSR) for this study, but may be pooled with biomarker data from other studies to generate hypotheses for future studies.

Patient reported outcomes (PRO) data will be collected to explore the effect of AZD6094 on disease-related symptoms and health-related quality of life (HRQoL). This exploratory analysis may be reported separately.

4. SUBJECT SELECTION CRITERIA

4.1 Inclusion criteria

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

1. Provision of informed consent prior to any study specific procedures, sampling and analyses. If a patient declines to participate in any voluntary exploratory research and/or genetic component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

2. Histologically confirmed papillary renal cell cancer, which is locally advanced or metastatic.

3. Availability of an archival tumour sample or a pre-treatment fresh tumour sample for confirmation of PRCC by a central laboratory and other biomarker (see Section 6.9). Baseline confirmation of PRCC may be performed locally in order to meet the eligibility criteria.

4. Treatment naïve or have failed on previous treatment for PRCC. Previous treatments may include: targeted therapy (i.e. sunitinib, sorafenib, bevacizumab, pazopanib, temsirolimus, and everolimus), traditional immunotherapy (i.e. interferon-α, interleukin-2), chemotherapy or a combination of chemoimmunotherapy.

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

6. At least one lesion, not previously irradiated, and not chosen for a biopsy if performed during the screening period that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

7. Adequate haematological function defined as:

   - Absolute neutrophil count (ANC) ≥1500/μL
   - Haemoglobin (Hgb) ≥9 g/dL
   - Platelets ≥100,000/μL

8. Adequate liver function defined as:

   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN)
   - Total bilirubin ≤1.5 x ULN (if patient has known Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin, bilirubin may be elevated ≤3 x ULN, but liver function tests must be within normal range)

9. Adequate renal function defined as glomerular filtration rate (GFR) ≥ 40 mL/min, as assessed using the standard methodology at the investigating centre (e.g. Cockcroft-Gault, MDRD or CKD-EPI formulae, EDTA clearance or 24-hour urine collection).

10. Adequate coagulation parameters, defined as International Normalisation Ratio (INR) <1.5 x ULN or activated partial thromboplastin time (aPTT) <1.5 x ULN. This applies only to patients who do not receive therapeutic anti-coagulation.

11. Patients with known tumour thrombus or deep vein thrombosis (DVT) are eligible if stable on low molecular weight heparin (LMWH) for ≥2 weeks.

12. Females should be using adequate contraceptive measures (Section 5.1), should not be breast feeding, and must have a negative pregnancy test prior to start of dosing if of childbearing potential or must have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:

- Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
- Women under the age of 50 years would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution.

13. Male patients should be willing to use barrier contraception, i.e. condoms.

14. Ability to swallow and retain oral medications.

15. Predicted life expectancy ≥12 weeks.

16. Aged at least 18 years.

17. Willingness and ability to comply with study and follow-up procedures.

18. Ability to understand the nature of this study and give written informed consent.

4.2 Exclusion criteria

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

1. Most recent chemotherapy, immunotherapy, chemo-immunotherapy, or investigational agents <21 days of the first dose of study treatment. Most recent targeted therapy <14 days of the first dose of study treatment.

2. Unresolved toxicities from any prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment with the exception of alopecia.

3. Prior or current treatment with a cMet inhibitor (e.g. Foretinib, Crizotinib, Cabozantinib, Onartuzumab). Patients with limited exposure may be discussed with the study medical monitor.

4. Strong inducers or inhibitors of CYP3A4, strong inhibitors of CYP1A2, or CYP3A4 substrates with a narrow therapeutic range within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort) Appendix I.

5. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy.

6. Major surgical procedures ≤28 days of beginning study drug or minor surgical procedures ≤7 days. No waiting is required following port-a-cath placement.

7. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks previously and there is no evidence of central nervous system disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy.

8. Current leptomeningeal metastases or spinal cord compression due to disease.

9. Acute or chronic liver or pancreatic disease.

10. Uncontrolled diabetes mellitus.

11. Gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhoea Grade ≥2, and malabsorption syndrome) actively present.

12. Any of the following cardiac diseases currently or within the last 6 months:

    - Unstable angina pectoris
    - Congestive heart failure (New York Heart Association [NYHA] ≥ Grade 2 [Appendix H])
    - Acute myocardial infarction
    - Stroke or transient ischemic attack

13. Inadequately controlled hypertension (i.e., systolic blood pressure [SBP] >160 mmHg or diastolic blood pressure (DBP) >100 mmHg) (patients with values above these levels must have their blood pressure (BP) controlled with medication prior to starting treatment).

14. Mean resting correct QT interval (QTc) >470 msec obtained from triplicate ECGs.

15. Any clinically important abnormalities in rhythm, conduction or morphology of resting electrocardiograms (ECGs), e.g. complete left bundle branch block, third degree heart block, second degree heart block, PR interval >250 msec.

16. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital or familial long QT syndrome, or family history of unexplained sudden death under 40 years of age, or any concomitant medications known to prolong QT interval.

17. Currently receiving treatment with therapeutic doses of warfarin sodium. Low molecular weight heparin (LMWH) is allowed.

18. Serious active infection at the time of treatment, or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment.

19. Known diagnosis of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C.

20. Presence of other active cancers, or history of treatment for invasive cancer ≤5 years. Patients with Stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.

21. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions apply while the patient is receiving AZD6094 and for the specified times before and after:

Pregnancy and conception

All patients must be made fully aware of the information relating to the potential for reproductive toxicity as detailed in the Informed Consent Form.

- Women of childbearing potential

  Females of childbearing potential should use reliable methods of contraception from the time of screening until 4 weeks after discontinuing study treatment.

Acceptable methods of contraception include abstinence, tubal ligation, combined oral, transdermal or intra-vaginal hormonal contraceptives, medroxyprogesterone injections (e.g. Depo-provera), copper-banded intra-uterine devices, hormone impregnated intra-uterine systems and vasectomised partners. All methods of contraception (with the exception of total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse.

- Males

  Male patients must use a condom during sexual intercourse with all sexual partners including a pregnant female partner during the study and for 4 weeks after discontinuing study treatment. However, where a sexual partner of a male participant is a woman of childbearing potential who is not using effective contraception, men must use a condom during sexual intercourse during the study and for 6 months after discontinuing study treatment.

  Male patients should avoid procreation during the trial and for 6 months after discontinuing study treatment.

  Male patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment.

Herbal preparations/medicines

Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (three weeks for St John's wort).

Acetaminophen (Paracetamol)

The administration of acetaminophen (paracetamol) to a patient is restricted to 3 grams per day or the maximum dose approved locally (if less than 3 gm/day) during the study.

Food restrictions

Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g. grapefruit juice or marmalade) during the study **(**e.g., no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1-2 teaspoons (15g) of Seville orange marmalade daily.

UV exposure

During AZD6094 therapy and for 4 weeks after the last dose patients should be advised to avoid prolonged exposure to the sun, wear protective clothing, a hat and seek shade from the sun as far as possible; in addition SP30+ sunscreen should be used. Exposure to other sources of UV light including sunbeds and tanning booths, etc. should be avoided.

5.2 Subject enrolment

The Principal Investigator (PI) or designee will:

1. Obtain signed informed consent from the potential subject before any study specific procedures are performed.

2. Assign potential subject a unique enrolment number.

3. Determine subject eligibility. See Sections 4.1 and 4.2

Investigators should discuss potential alternative treatments with all patients interested in participating in the trial.

If a subject withdraws from participation in the study, then his/her enrolment code cannot be reused.

Every effort should be made to minimise the time between enrolment and starting treatment.

5.3 Procedures for handling subjects incorrectly enrolled

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

Where patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the Investigator should inform the International Study Chair or Medical Monitor immediately. The decision on when to discontinue the ineligible patient from the study is based on the medical/safety risk for the patient. The International Study Chair or Medical Monitor is to ensure all such contacts are appropriately documented.

For patients who are correctly enrolled based on a positive local PRCC assessment but subsequently are deemed negative on central review, the decision regarding whether the patient should continue to receive treatment or not will be based upon the Investigator's opinion in conjunction with the International Study Chair or Medical Monitor.

5.4 Treatments

5.4.1 Identity of investigational product(s)

AstraZeneca will supply AZD6094 tablets for oral use. The tablets can be supplied at 2 strengths, 100 and 200 mg, in open-labelled high-density polyethylene (HDPE) bottles, which sufficiently protect the drug from light. The different tablet strengths should not be dispensed from the bottles or combined in the same bottle at any time. Additional information about the investigational product may be found in the IB.

Investigational product	Dosage form and strength	Manufacturer
AZD6094	100 mg and 200 mg tablets	

5.4.2 Doses and treatment regimens

AZD6094 600 mg PO QD will be administered in 21-day (3-week) treatment cycles. Alternative schedules e.g. continuous twice daily dosing, and/or changes in dose may be instigated in response to emerging safety, tolerability, or PK data from this study and any ongoing studies.

AZD6094 is to be administered under fed conditions, which is defined as administration of study drug to the patient within 1 hour after the start of a meal. The time of day for administration of AZD6094 should be consistent. The current feeding restriction may be lifted if supported by emerging data from an ongoing clinical study (Study D5081C00004 – NCT02017236), which is investigating the effect of food on the PK of AZD6094.

On scheduled PK collection days the patient should be instructed to wait until he/she arrives at the study centre to take their study drug and food when instructed.

If the patient misses a dose of study drug, the patient should take the dose as soon as possible, but not less than 12 hours before the next dose is due.

If vomiting occurs after taking the study drug, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of AZD6094. If vomiting persists, the patient should contact the Investigator. AZD6094 dosing compliance should be reviewed with the patient at the beginning of each new treatment cycle when study drug is dispensed. In addition, patients should be advised to return any unused AZD6094 in the original bottles, in addition to returning any empty bottles.

All study drugs must be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and the IB specifies the appropriate storage.

5.4.3 Labelling

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

5.4.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

5.5 Dose modifications

Toxicity will be assessed utilizing the NCI CTCAE v4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), unless otherwise specified. Management of investigational product related toxicities is described in Section 1.4.2, which includes risk minimisation activities for the key potential risks associated with AZD6094.

5.5.1 AZD6094 dose modification and guidance

AZD6094 is expected to be generally well tolerated. Substantial acute toxicities should be managed as medically indicated and with temporary suspension of study drug, as appropriate. Dose reductions or holds are allowed as clinically indicated by the treating physician and in line with Table 1 and Table 2. For each patient, a maximum of 2 dose reductions will be allowed. Guidance on dose level reduction is presented in Table 1.

Table 1 AZD6094 dose level modification

Dose level	AZD6094 PO daily dose
Starting Dose	**600 mg QD**
-1 Dose Level	400 mg QD
-2 Dose Level	200 mg QD

5.5.2 Dose modifications due to haematologic and non-haematologic toxicity

Dose reduction guidelines for haematologic and non-haematologic toxicities are shown in Table 2. If ≥Grade 3 toxicity that is expected to be manageable and reversible with a dose reduction occurs, treatment should be held until toxicity resolves to ≤ Grade 1. Study drug should be permanently discontinued in any patient with ≥Grade 3 haematologic or non-haematologic toxicity lasting ≥7 days that does not resolve to ≤Grade 1 within 2 weeks.

Table 2 Dose modifications for haematologic and non-haematologic toxicities

NCI CTCAE v4.03 Toxicity Grade	Action
Grade 0, 1, or 2	**None**
Grade 3 or 4 Expected manageable/reversible with dose reduction	Hold[a]
Toxicity remains Grade ≥ 3 for >7 days	Discontinue study drug
Toxicity lasts ≥ 7 days and resolves to ≤ Grade 1	Reduce one dose level

Table 2 Dose modifications for haematologic and non-haematologic toxicities

NCI CTCAE v4.03 Toxicity Grade	Action
Grade 0, 1, or 2	**None**
Recurrence of Grade 3	Hold[a]
Toxicity remains Grade ≥ 3 for >7 days	Discontinue study drug
Toxicity lasts ≥ 7 days and resolves to ≤ Grade 1	Reduce one dose level or discontinue study drug[a]
Recurrence of Grade 4	Discontinue study drug
Grade 3 or 4 (new or recurrent) Not expected to be manageable/reversible with dose reduction	Discontinue study drug

[a] Study drug should be held until toxicity resolves to ≤ Grade 1. Study drug should be discontinued in any patient with ≥Grade 3 haematologic or non-haematologic toxicity lasting ≥7 days that does not resolve to ≤Grade 1 within 2 weeks.

5.6 Concomitant medication

All concomitant medications and significant non-drug therapies taken ≤28 days prior to the start of study drug should be recorded in the eCRF.

Supportive care and other medication, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

The administration of acetaminophen (paracetamol) to a patient is restricted to 3 grams per day or the maximum dose approved locally (if this is less than 3 gm/day) during the study. In addition, Investigators should review the patient's concomitant medications, and evaluate the need for the patient to continue on hepatic metabolism modifying agents, such as statins.

Based upon studies of *in vitro* liver microsomes and S9 fractions, AZD6094 is metabolized by several metabolic enzymes, including both CYP450 enzymes and some NADPH independent non-CYP enzymes. Patients receiving strong inducers or strong inhibitors of CYP3A4, strong inhibitors of CYP1A2, or CYP3A4 substrates which have a narrow therapeutic range within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort) will be excluded. Concomitant use of drugs that are known to be strong inducers of CYP3A4, strong inhibitors of CYP3A4 or CYP1A2, CYP3A4 substrates which have a narrow therapeutic range or CYP3A4 sensitive substrates during the trial should be avoided as far as possible unless considered essential by the investigator, in which case patients must be monitored closely for potentially reduced efficacy or increased toxicity due to drug-drug interactions (Appendix I).

AZD6094 is a weak competitive inhibitor of CYP2C8 (IC_{50}=9.1μM). Those drugs defined as strong CYP2C8 substrates (almost exclusively metabolised by CYP2C8, such as Repaglinide and Rosiglitazone) should be used with caution. AZD6094 is not a substrate of Pgp but is a

weak inhibitor in vitro (IC_{50}=17.9μM). Drugs that are known to be affected by Pgp such as digoxin, quinidine, loperamide, ritonavir and saquinavir should be used with caution.

5.6.1 Permitted Concomitant Medications and Treatments

Blood transfusions are allowed during the study.

Patients are permitted to receive granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) in accordance with the American Society of Clinical Oncology's (ASCO) guidelines. Use of erythropoietin is allowed.

Patients may receive bisphosphonates and/or RANK ligand inhibitors like denosumab, or corticosteroids for the treatment of bone metastases.

Patients may receive palliative radiotherapy for painful bone metastases. The radiation field cannot encompass a target lesion.

5.6.2 Prohibited Concomitant Medications and Treatments

No other investigational therapy should be given to patients. No anticancer agents should be given to patients other than the study drugs. If such agents are required for a patient, then the patient must first be withdrawn from the study.

Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drugs, (3 weeks for St John's wort).

Refer to Appendix I for concomitant medications that should be restricted or used with caution.

5.7 Treatment compliance

The administration of AZD6094 should be recorded in the appropriate sections of the eCRF.

5.7.1 Accountability

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

If a patient misses any AZD6094 dose either through poor adherence or, for example, due to vomiting, this dose will not be made up and the patient will be asked to take the next dose at the next scheduled time point.

Patients must return all unused medication and empty containers to the Investigator.

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

5.8 Screening failures

Screening failures are patients who do not fulfil the eligibility criteria for the study and are therefore not enrolled. These patients should have their reason for study withdrawal recorded as 'Eligibility Criteria not fulfilled' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screening failures (not enrolled patients).

5.9 Discontinuation of investigational product

Subjects may be discontinued from AZD6094 in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Pregnancy
- Severe non-compliance to study protocol
- Confirmed disease progression
- Patients incorrectly initiated on investigational product (Section 5.3)
- Development of any study specific criteria for discontinuation
- If Investigator considers a patient should not be continued or included in the trial

5.9.1 Procedures for discontinuation of a subject from investigational product

A subject that decides to discontinue AZD6094 will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (see Sections 6.4.3 and 6.4.4); and all study drugs should be returned by the subject.

If a subject is withdrawn from study, see Section 5.10.

5.10 Withdrawal from study

Subjects are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will

be seen and assessed by an Investigator. Adverse events will be followed up (see Sections 6.4.3 and 6.4.4); and all study drugs should be returned by the subject.

If a subject withdraws from the study, then his/her enrolment code cannot be reused.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Trial Master electronic data base (EDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the electronic eCRFs as specified in the study protocol and in accordance with the instructions provided.

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

Table 3 Study plan

	Screening – Baseline[b]	AZD6094 Continuous Dosing											Discon-tinuation of IP[v]	Follow-Up	
		Cycle 1 Day			Cycle 2 Day			Cycle 3 Day			Every 6 Weeks	Cycle 4 & beyond		Progression Free Survival[w]	Survival Follow-Up[x]
		1	8	15	1	8	15	1	8	15		Day 1			
Visit	1	2	3	4	5	6	7	8	9	10		11			
Day	-28 to 0	1	8	15	22	29	36	43	50	57		64			
Activity Visit Window		0	±1d	±1d	±2d	±1d	±1d	±3d	±1d	±1d	±7days	±3d			
Informed consent[a]	X														
Demography[c]	X														
Medical/surgical history[d]	X												X		
Physical examination	X				X			X				X	X		
Vital signs[e, y]	X	X	X	X	X			X				X	X		
Archival tumour sample for PRCC confirmation[f]	X														
ECOG Performance Status	X	X			X			X				X	X		
Haematology[y]	X[g]	X	X	X	X			X				X	X		
Clinical Chemistry[y, z]	X	X	X	X	X	X	X	X	X	X		X	X		
Coagulation	X[h]														
Urinalysis[i, y]	X	X	X	X	X			X				X	X		
Pregnancy test (for women of childbearing potential)[j]	X	X[j]											X		
12-lead ECG (triplicate)[k,y]	X				X			X					X		
Echocardiogram/MUGA Scan	X	12 weekly (±1 week) relative to first dose ⟷													
Tumour paired biopsies	X[l]		X[l]										X[l]		
PGx whole blood sample[n]	X														
PK blood collection[o] Primary Designated PK Sites			X[m]	X	X			X				X			

Table 3 Study plan

	Screening – Baseline[b]	AZD6094 Continuous Dosing											Discon-tinuation of IP[v]	Follow-Up	
		Cycle 1 Day			Cycle 2 Day			Cycle 3 Day			Every 6 Weeks	Cycle 4 & beyond		Progression Free Survival[w]	Survival Follow-Up[x]
		1	8	15	1	8	15	1	8	15		Day 1			
Visit	1	2	3	4	5	6	7	8	9	10		11			
Day	-28 to 0	1	8	15	22	29	36	43	50	57		64			
Activity Visit Window		0	±1d	±1d	±2d	±1d	±1d	±3d	±1d	±1d	±7days	±3d			
PK urine collection Primary Designated PK Sites				X[q]											
PK sample collection[p] Secondary Designated PK sites			X	X	X			X				X[p]			
ctDNA plasma sample collection[r]	X	X						X			X		X		
Circulating biomarker sample collection[s]	X	X	X					X			X		X		
Tumour Assessment per RECIST v1.1[t]	X										X		X	X	
Patient Reported Outcomes[u]		X			X			X[u]			X[u]		X[u]		
Hospital resource use		X			X			X[u]			X[u]		X		
Concomitant Medications	X	X	X	X	X			X				X	X	X	X
Adverse Events		X	X	X	X			X				X	X	X	
AZD6094 Administration		→													

[a] Written informed consent must be obtained before any screening or baseline activities occur.

[b] Screening activities will occur ≤28 days prior to initiation of study drug.

[c] Patient characteristics including demographic information (age, sex, race, and ethnicity) will be collected.

[d] Relevant medical history and current medical conditions including cancer history (prior cancer therapies, radiation therapy, and surgery(ies), and related symptoms must be recorded in the appropriate eCRFs.

[e] Vital signs include: heart rate, systolic and diastolic blood pressure, respiration rate, weight, height [only at screening] and temperature.

[f] An archival (or fresh is archive sample is not available) tumour sample is mandatory for this study (see Section 6.9).

[g] Screening bloods can be done in the fed or fasted state.

[h] If INR, PTT are normal at baseline, they do not need to be repeated. Patients requiring the initiation of an anti-coagulation therapy during study treatment should have their coagulation test performed according to standard management guidelines.

[i] Urinalysis: Dipstick first, then microscopy if any abnormal findings. If 3+ or greater proteinuria is identified by dipstick assessment, a 24-hour urine collection for formal quantification of the level of protein excretion should be performed.

[j] Women of childbearing potential will have serum or urine pregnancy tests at screening, pre-dose Cycle 1 Day 1 and at treatment discontinuation.

[k] Triplicate ECGs will be performed at baseline, at Cycle 2 Day 1, Cycle 3 Day 1, at the end of study treatment and at other times if clinically indicated.

[l] Baseline or Cycle 1 Day 1 pre-dose, and Cycle 1 Day 8 optional tumour biopsies will be analysed for PDc effect of AZD6094. Cycle 1 Day 8 tumour biopsy should be collected at 2-3 hours post-dose. If the Cycle 1 Day 8 time is not suitable for the patient, contact the Sponsor to arrange for the next best time point. Additional collection of an optional tumour biopsy at disease progression will be analysed to understand the mechanism of resistance to AZD6094. Analysis will be performed at a Sponsor or central laboratory (see Section 6.10).

[m] PK sample should be collected at time of tumour biopsy on Cycle 1 Day 8, 2-3 hours post dose (see Section 6.10).

[n] A 10 ml blood sample for genetic research will be obtained from the patient at screening prior to the first administration of AZD6094. If for any reason the sample is not drawn prior to dosing it may be collected at any visit until the last visit. Only one sample will be collected (see Section 6.8.1).

[o] PK sampling schedule for patients at **Primary Designated PK Sites** (see Section 6.6.1, Table 5). Blood sample (4 mL) to be collected on pre-dose Cycle 1 Day 8, pre-dose Cycle 1 Day 15 and post-dose at 30 minutes, 1, 2, 3, 4, 6 and 8 hours. Cycle 2, 3 and 4 Day 1 a pre-dose sample should be collected.

[p] PK sampling schedule for patients at **Secondary Designated PK Sites** (see Section 6.6.1, Table 7). Blood sample (2 mL) to be collected on pre-dose Cycle 1 Day 8, pre-dose Cycle 1 Day 15 and post-dosing at 1 and 4 hours. Cycle 2, 3 and 4 Day 1 a pre-dose sample should be collected.

[q] PK urine sampling applies only to patients at **Primary Designated Sites** (see Section 6.5, Table 6). Collect sample 0-4 hours and 4-8 hours post-dosing.

[r] ctDNA plasma sample collected at screening, pre-dose Cycle 1 Day 1, every odd cycle day 1 (Cycle 3 Day 1, Cycle 5 Day 1 etc) corresponding with RECIST v1.1 tumour assessments, at discontinuation of treatment and at disease progression (only if patient continues after discontinuation of AZD6094) (see Section 6.7.1).

[s] A serum circulating biomarker sample will be collected at screening, pre-dose Cycle 1 Day 1, pre-dose Cycle 1 Day 8, Week 6 and Week 12 (corresponding with RECIST v1.1 tumour assessments), at discontinuation of treatment and at disease progression (only if patient continues after discontinuation of AZD6094) (see Section 6.7.1).

[t] Baseline tumour imaging studies (e.g. CT scan of the chest and abdomen/pelvis) will be performed within 28 days prior to the first dose of study drug and will be repeated every 6 weeks relative to 1st day of dosing ([±7 days] or two cycles) for the first 12 months and then 12 weeks thereafter until objective disease progression or withdrawal from the study. The same method of assessment and the same technique must be used to characterise each identified and reported lesion at baseline and during subsequent imaging procedures.

[u] PROs (FACT-G, FKSI-19, EQ-5D-5L) at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and every 6 weeks thereafter, at treatment discontinuation (see Section 6.5). Hospital resource use to be captured on a similar interval.

[v] A treatment discontinuation visit will be conducted as soon as possible for study assessments after the patient received the last dose of AZD6094. In addition a safety follow-up will be performed with the patient 30 +/-7 days after the discontinuation of AZD6094, to follow-up on any SAE/AE's and concomitant medications (including any subsequent cancer therapy). Patients will be followed during the off study period until all treatment related toxicity resolve (see Section 6.2.3).

[w] Patients discontinuing treatment prior to documented disease progression will also enter progression free survival follow-up period where they will continue to have disease assessments every 6 weeks for the first 12 months (of study drug) and then every 12 weeks thereafter until disease progression, death, loss to follow-up or withdrawal of consent, whichever comes first. Anti-cancer therapies will be recorded for patients discontinuing treatment prior to documented disease progression entering the survival follow-up period.

[x] Patients discontinuing treatment due to documented disease progression will enter survival follow-up period, where they will be followed for the initiation of subsequent anti-cancer therapies every 3 months until death, loss to follow-up or withdrawal of consent, whichever comes first.

[y] Vital signs, ECGs, urinalysis, haematology, and clinical chemistry samples should be taken pre-dose on days the patient visits the clinic for study assessments.

[z] Blood liver functions will be monitored closely during Cycles 1-3 with the weekly collection of a serum clinical chemistry panel.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment procedures

At screening (Visit 1), each potential patient will provide informed consent prior to starting any study specific procedures (see Table 3).

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

Demographic data and other characteristics will be recorded and will include: age, sex, race and ethnicity according to local regulations.

A standard medical history (including prior cancer therapies, radiation therapy, and current medical conditions) as weel as medication and surgical history will be obtained along with review of the selection criteria with the patient.

Each patient will undergo screening according to the study plan (Table 3) during the 28 days prior to admission to confirm eligibility (see Sections 4.1 and 4.2). Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided the assessments fall within the protocol specified period prior to the first dose of study treatment.

6.2.2 Treatment procedures

Treatment procedures will be performed as detailed in the Study Plan (Table 3) and in the following sections.

6.2.3 Follow-up procedures

A post study assessment will be performed at the time investigational product is permanently discontinued (see Table 3).

In addition for safety follow-up as a minimum, telephone contact should be made with the patient 30 (+/-7) days after the discontinuation of AZD6094 to follow up on any SAE/AE's and concomitant medications (including any subsequent cancer therapy). The primary purpose is to follow-up any AEs ongoing at the time of discontinuation and to assess any new AEs that may have occurred since discontinuation. Any AE/ SAE/ abnormal laboratory findings that are ongoing at the time of study treatment discontinuation or any new treatment related events within 30 days of last study treatment, must be followed up to resolution or until the event becomes stable (or returns to baseline) or is unlikely to resolve further in the opinion of the Investigator.

Patients discontinuing treatment prior to documented disease progression will also enter survival follow-up period where they will continue to have disease assessments every 6 weeks for the first 12 months (of study drug) and then every 12 weeks thereafter until disease progression, death, loss to follow-up or withdrawal of consent, whichever comes first.

Patients discontinuing treatment due to documented disease progression will enter survival follow-up period, where they will be followed for the initiation of subsequent anti-cancer therapies every 3 months until death, loss to follow-up or withdrawal of consent, whichever comes first.

6.3 Efficacy

Tumour Assessments

RECIST 1.1 criteria will be used to assess patient response to treatment by ORR, PFS and OS. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are presented in Appendix F.

The methods of assessment of tumour burden used at baseline – CT or MRI scans – for chest, abdomen and pelvis must be used at each subsequent follow-up assessment.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 6 weeks (±7 days), for the first 12 months and every 12 weeks thereafter until objective disease progression as defined by RECIST v1.1.

Categorisation of objective tumour response assessment will be based on the RECIST v1.1 criteria of response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

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

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

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Table 3.

All RECIST 1.1 assessment images will be reviewed at site. Duplicates may be collected and stored by an AZ appointed representative, and sent for independent central RECIST 1.1 review, if deemed appropriate.

6.3.1 Efficacy variable

Each patient will undergo screening (see Table 3) during the 28 days prior to admission to confirm eligibility. Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided the assessments fall within the protocol specified period prior to the first dose of study treatment. Tumour assessments by CT or MRI scan should be obtained within 4 weeks of starting treatment.

6.4 Safety

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

6.4.1 Definition of adverse events

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

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

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase that fulfils one or more of the following criteria:

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

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from time of signature of informed consent throughout the treatment period and including the 30-day follow-up period after discontinuation of study drug.

SAEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

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

Variables

The following variables will be collect for each AE;

- AE description
- The date when the AE started and stopped
- CTCAE grade and changes in grade during the course of the AE
- Whether the AE is serious
- Causality rating against the investigational product (IP) or procedure (yes or no)
- Action taken with regard to IP
- Outcome

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Reason AE is serious
- Date of hospitalisation
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of AE.

The grading scales found in the revised NCI CTCAE v4.03 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria should be utilised that converts mild, moderate and severe events

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality collection

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

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

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

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

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

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

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

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

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

Disease progression

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

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF and submitted via SAE paper report form.

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

SAE information will be sent via secure e-mail connection or via fax. The Safety Department standard paper SAE Report with supporting relevant source documents (e.g. history and physical [H&P], hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed to evaluate the event) will be attached and sent via:

The designated Safety Department representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one business day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Safety Department representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

AstraZeneca or their representative will provide Regulatory Authorities, Ethics Committees and PIs with clinical safety updates/reports according to local requirements.

The reference document for definition of expectedness is Section 5.4 of the Investigators' Brochure for AZD6094

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the study plan (refer to Table 3) and will be performed locally, unless otherwise noted. Laboratory reports from scheduled and unscheduled assessments should be reviewed for potential Hy's law cases throughout the study treatment period and up to and including 30 days after study treatment discontinuation.

The following laboratory variables will be measured:

Table 4 Standard laboratory safety assessment panel

Clinical chemistry safety	**Haematology**
S/P-Albumin	B-Haemoglobin
S/P-ALT	B-Leucocyte cell count
S/P-AST	B-Absolute leucocyte differential count:
S/P-Alkaline phosphatase	B-Neutrophils
S/P-Bilirubin, total	B-Lymphocytes
S/P-Calcium, total	B-Eosinophils
S/P-Creatinine	B-Platelet count
S/P-Glucose	
S/P-Sodium	**Urinalysis***
S/P-Magnesium	U-Glucose
S/P-Potassium	U-Protein
S/P-Total Protein	U-Blood
S/P-Urea nitrogen	U-Ketones
S/P- Lactate dehydrogenase	U-Microscopy (red blood cells and white blood cells, bacteria, casts and crystals) only perform if urinalysis is abnormal
S/P- Thyroid Stimulating Hormone	
S/P- Free T4	

S = serum; B = blood; P = plasma; U = urine

*If 3+ or greater proteinuria is identified by dipstick assessment, a 24-hour urine collection for formal quantification of the level of protein excretion should be performed.

Additionally a serum/ urine sample will be collected from all WoCBP at screening, Cycle 1 Day 1 and at treatment discontinuation.

Unscheduled blood or urine samples may need to be taken at onset and as a part of a follow-up of some SAEs. The results should be added to clinical trial database.

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

For blood volume see Section 7.1.

6.4.6 Physical examination

A complete physical examination will be performed taken at the times indicated in the study plan (refer to Table 3).

6.4.7 Performance status

Performance status will be assessed at screening, prior to the first dose of study treatment, at the beginning of each Cycle, and at discontinuation according to ECOG criteria as follows:

0 = Fully active, able to carry out all pre-disease activities without restrictions

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light housework, office work

2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair

6.4.8 Tumour assessments

Baseline tumour imaging studies (e.g., CT scan of the chest and abdomen/pelvis) will be performed within 28 days prior to the first dose of study drug and will be repeated every 6 weeks (±7 days) for the first 12 months and then every 12 weeks thereafter until objective disease progression as defined by RECIST v1.1. Additional imaging may be performed based on individual patient signs and symptoms. The same method of assessment and the same technique must be used to characterise each identified and reported lesion at baseline and during subsequent imaging procedures. All patients who respond to treatment (complete response [CR] or partial response [PR]) or have stable disease (SD) will continue to receive AZD6094 until they develop progressive disease (PD) or unacceptable toxicity.

6.4.9 Electrocardiograms

Electrocardiograms (ECGs) will be performed at baseline, Cycle 2 Day1, Cycle 3 Day1 as indicated in the study plan (Table 3) and will be repeated at the end of study treatment and whenever clinically indicated. Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. For each time point three ECG recordings should be taken at about 5 minute intervals. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

6.4.10 Vital signs

Measurements should be taken at approximately the same time of the day at each visit.

Vital signs (heart rate, systolic and diastolic blood pressure, respiration rate, weight, height [only at screening] and temperature) will be assessed at the times indicated in the study plan (see Table 3).

6.4.11 Echocardiogram/ MUGA Scan

An Echocardiogram or MUGA scan to assess LVEF will be conducted at Screening – Baseline, and 12-weekly thereafter (±1 week). The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans if required. The patients should also be examined using the same machine and operator whenever possible.

6.5 Administration of patient reported outcomes

Patient reported outcome questionnaires will be administered using paper questionnaires.

All patients should complete the questionnaire Functional Assessment of Cancer Therapy Kidney Symptom Index-19 (FKSI-19), Functional Assessment of Cancer Therapy – General (FACT-G) and European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) at the scheduled clinic visit at Cycle 1 Day 1 pre-dose, and throughout the study at the times specified in the study plan (Table 3). The patient should also complete the questionnaire at progression.

If any scheduled PRO assessment is not completed the reason for non-completion should be recorded.

PROs will be filled out prior to any other site activities and encounters with the study physician. The patients will be instructed to complete the PROs independently. The site will have a designated quiet space for patients to use when completing the assessments. Each centre should allocate responsibility for PRO assessment to a specified individual (e.g. a research nurse).

It is important that the value and relevance of PRO data are explained carefully to participating patients so that they are motivated to comply with data collection. The research nurse or appointed individual should also stress that the information is confidential. If the patient has any medical problems he/she should discuss them with the doctor or research nurse separately from their PRO assessment.

The instructions for completion of questionnaires are as follows:

- The questionnaires must be completed before any investigations or discussions about the status of the patient's disease with the clinic staff.
- The patient must complete the questionnaires themselves without any intervention from family, friends, centre staff etc.

- The only exception to this is if the patient is blind or illiterate. In this case the questionnaires may be read to the patient verbatim, however the reader must not aid in the interpretation of questions or in the selection of answers.
- Only one answer to every question should be checked.
- Centre personnel should not review the responses to the questionnaires with the patient or with any other centre staff.

Following completion, the nurse or appointed individual may quickly scan the questionnaires visually for completeness and should confirm verbally with the patient that the questionnaires have been completed fully.

6.5.1 Functional Assessment of Cancer Therapy – General

The validated Functional Assessment of Cancer Therapy-General (FACT-G) (now in Version 4) is a 27-item instrument divided into four primary QOL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. It is considered appropriate for use with patients with any form of cancer (Appendix G).

6.5.2 Functional Assessment of Cancer Therapy Kidney Symptom Index-19

The Functional Assessment of Cancer Therapy Kidney Symptom Index-19 (FKSI-19) is a validated instrument designed to accurately assess patient self-reported symptom burden to determine treatment impact and evaluate clinical benefit in patients with renal cancer (Rao et al 2009).

The instrument includes 19 items covering 4 subscales: Disease-Related Symptoms Subscale – Physical, Disease-Related Symptoms Subscale – Emotional, Treatment Side Effects Subscale, Function and Well-Being Subscale; responses are reported as it applies to the past 7 days (Appendix G).

6.5.3 European Quality of Life-5 Dimensions-5 Levels

The EQ-5D-5L is a standardised measure of health status developed by the EuroQol Group in order to estimate a simple, generic measure of health state utility for economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. It includes five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) plus a visual analogue scale (thermometer) asking the patient to rate their health today (Appendix G).

6.6 Pharmacokinetics

6.6.1 Collection of samples

Approximately 20 centres in the EU and North America are planned to enrol PRCC patients. Centres assigned as “Primary Designated PK Sites” will take venous blood samples (4 mL) at the times detailed in Table 5 for determination of plasma concentrations of AZD6094, and of M2 and M3, major metabolites of AZD6094 from a minimum of 12 patients. For “Primary

Designated PK Sites" the decision to revert to the PK schedule adopted by "Secondary Designated PK Sites" will be made following a review of data by the Steering Committee. The date and actual time of the PK sample will be recorded. The samples will be taken split into 2 x 2 ml samples, one used for PK analysis and one may be used for metabolite identification purposes. If the dosing regimen is altered, the PK sampling regimen will be appropriately amended to characterise PK profiles.

In addition, centres assigned as "Primary Designated PK Sites" will take a urine sample (2 ml) from the total urine volume collected from 0-4 hours and 4-8 hours post-dose in Cycle 1 Day 15 from patients (Table 6). The date and actual time of urine collection and the weight of the collection will be recorded.

Centres assigned as "Secondary Designated PK Sites" will take venous blood samples (2 ml) from patients at the times detailed in Table 7 for determination of plasma concentrations of AZD6094, and of M2 and M3, major metabolites of AZD6094. The date and actual time of the PK sample will be recorded. If the dosing regimen is altered, the PK sampling regimen will be appropriately amended to characterise PK profiles. No urine samples will be collected from these patients.

Samples for the determination the concentrations of AZD6094, and major metabolites M2 and M3 in plasma will be analysed by on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

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

Table 5 Pharmacokinetic blood sampling schedule – patients at Primary Designated PK Sites*

Day	Time for blood sample collection (4 mL)
Cycle 1 Day 8 (only for patients undergoing tumour biopsy)	Single Sample: Pre-Dose Single Sample: Post-Dose sample 2-3 hours at time of biopsy
Cycle 1 Day 15	AZD6094 sampling: Pre-Dose, 0.5, 1, 2, 3, 4, 6, and 8 hours post-dosing
Cycle 2, 3 and 4 Day 1	Single Sample: Pre-Dose

* Time of ingestion of tablet the day before visit day to be recorded on the CRF

Table 6 Pharmacokinetic urine sampling schedule at Primary Designated PK Sites

Day	Time for urine sample collection
Cycle 1 Day 15	0-4 hr, 4-8 hr post-dosing

Table 7 Pharmacokinetic blood sampling schedule – patients at Secondary Designated PK Sites*

Day	Time for blood collection (2 ml)
Cycle 1 Day 8 (only for patients undergoing tumour biopsy)	Single Sample: Pre-Dose Single Sample: Post-Dose sample 2-3 hours at time of biopsy
Cycle 1 Day 15	AZD6094 sampling: Pre-Dose, 1 and 4 hours post-dosing
Cycle 2, 3 and 4 Day 1	Single Sample: Pre-Dose

* Time of ingestion of tablet the day before visit day to be recorded on the CRF

6.7 Blood-borne and circulating tumour DNA (ctDNA) biomarker samples

6.7.1 Collection of biomarkers

Serum blood-borne biomarkers

Blood samples (sample of 5 mL) for serum circulating biomarker will be taken at the times presented in Table 3.

Serum samples will be taken at the following times:

- Screening
- Pre-dose Cycle 1 Day 1
- Pre-dose Cycle 1 Day 8
- Week 6 (corresponding with first RECIST v1.1 tumour assessment)
- Week 12 (corresponding with first RECIST v1.1 tumour assessment)
- Discontinuation of treatment
- On progression (only if patient continues after discontinuation of AZD6094)

The samples will be analysed for a range of oncology biomarkers, which may correlate with drug response.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

Plasma ctDNA

Blood samples (sample of 10 mL) for plasma ctDNA will be taken at the times presented in Table 3.

Plasma samples will be taken at the following times:

- Screening
- Pre-dose Cycle 1 Day 1
- Every odd Cycle Day 1 (Cycle 3 Day 1, Cycle 5 Day 1 etc) corresponding with RECIST v1.1 tumour assessment
- Discontinuation of treatment
- On progression (only if patient continues after discontinuation of AZD6094)

ctDNA will be analysed to explore genetic tumour markers in plasma and their correlation with markers in tumour samples and to monitor for the emergence of resistance.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

6.8 Pharmacogenetics

If a patient agrees to participate in the host pharmacogenetics research component of the study a blood sample will be collected (Appendix D). The results of this pharmacogenetic research will be reported separately and will not form part of the Clinical Study Report.

6.8.1 Collection of pharmacogenetic samples

A 10 ml blood sample for genetic research will be obtained from the patient at screening prior to the first administration of AZD6094 in the study. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event. Such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn prior to dosing it may be taken at any visit until the last study visit. Only one sample will be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

6.9 Archival tumour samples

All patients will be required to provide an archived tumour sample at the time of enrolment to confirm eligibility by a central laboratory and perform other biomarker analysis. The availability of these tumour samples is mandatory for all patients enrolled in the study.

Representative formalin fixed, paraffin embedded (FFPE) tissue block(s) from initial diagnosis that contain enough tissue to generate 20 unstained slides should be provided along with an associated pathology report. In the absence of paraffin-embedded tissue block, a minimum of 12 unstained slides of paraffin-embedded tumour should be provided. If an archived tumour sample is not available a fresh tumour sample will be required.

Tumour samples will be analysed by histopathology to confirm tumour type. Tumour samples will also be analysed for genetic aberrations of MET, MET related genes, and MET protein expression.

See Laboratory Manual for handling and shipping instructions of the archival or fresh tumour samples to the central laboratory.

6.10 Tumour biopsies

Matched pre and post dose optional tumour paired biopsies (from the primary tumour or metastatic site) will be collected from consenting patients with easily accessible tumours. Biopsy samples will be collected pre-treatment at baseline. The second biopsy samples should be taken in a fasted state at Cycle 1 Day 8, at 2-3 hours post-dose; a PK sample will also be collected at this time (see Table 3). Biomarkers, relating to mode of action and response will be analysed. These will include, but are not limited to, total-cMet, phosphorylated-cMet. Local clinical practice should be followed for the number of hours fasted prior to the operating procedure to acquire a biopsy.

Patients with a previously confirmed objective response will have the option to provide a biopsy sample at disease progression to understand mechanisms of resistance to AZD6094.

All tumour biopsies will be collected, stored and shipped as detailed in the Investigator Laboratory Manual.

Any residual samples remaining after analysis will be retained for any potential subsequent retrospective analysis of other response related and/or cancer related biomarkers. It is not intended that data derived from residual sample analysis will be reported in the CSR.

Informed consent must be obtained from any patient who agrees to provide tissue for correlative testing.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The volume of blood that will be drawn from each patient during the study will vary depending upon the length of participation, patient consent to exploratory biomarker collections and, and standard practices.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of established methods. The number of samples/volumes is therefore subject to centre-specific changes. Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments or additional PK assessment.

The total volume of blood that will be drawn from each subject receiving a minimum of 24 weeks of IP in this study is as follows:

Table 8 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	8 ml	15	120
	Haematology	4 ml	11	44
	Coagulation	5 ml	1	5
Pharmacokinetics (Primary Designated PK Sites)*		4 ml	13	52
Pharmacokinetics (Secondary Designated PK Sites)**		2 ml	8	16
Blood-borne Biomarkers		5 ml	5	25
CtDNA		10 ml	6	60
PGx		10 ml	1	10
Total			48* 43**	284* 248**

7.2 Handling, storage and destruction of biological samples

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

Biological samples for future research can be retained at AstraZeneca for a maximum of 25 years following the last patient's last visit in the study. The results from future analysis will be reported separately and will not form part of the CSR.

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR, but separately in a Bioanalytical Report. Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. Samples may also be disposed of earlier, pending further notification.

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

7.2.2 Pharmacogenetic samples

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 25 years from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

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

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

7.3 Labelling and shipment of biohazard samples

The PI ensures that samples are labelled and shipped in accordance with the Laboratory Manual and if applicable: the Biological Substance, Category B Regulations (materials

containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

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

7.4 Chain of custody of biological samples

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

The PI at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

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

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

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

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

The PI:

- Ensures AstraZeneca is notified immediately of the patient's withdrawal of informed consent to the use of donated biological samples
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed/destroyed/repatriated, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed/repatriated and the action documented and returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed 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.

AstraZeneca ensures that biological samples are returned to the source at the end of a specified period as described in the informed consent.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject data protection

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

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.

8.3 Ethics and regulatory review

An EC should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff

Note: Ethics Committee is synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC) for the purposes of this protocol.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The EC should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC annually.

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

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory authorities, ECs and PIs with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each PI is responsible for providing the ECs/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

8.4 Informed consent

The PI(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided

Ensure each subject provides signed and dated ICF(s) before conducting any procedure specifically for the study

- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF(s) is given to the subject

- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF(s) that is approved by an EC.

8.5 Changes to the protocol and informed consent form

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

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

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

AstraZeneca representative or representative will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to EC see Section 8.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca representative and the centre's EC are to approve the revised ICF before the revised form is used.

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

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC 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, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca representative immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT

9.1 Pre-study activities

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

- Determine the adequacy of the facilities
- Determine availability of appropriate subjects for the study

- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA between AstraZeneca and the Investigator.

9.2 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 (CSP) and related documents with the investigational staff and also train them in any study specific procedures and the EDC system(s) utilised.

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

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

9.3 Monitoring of the study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g. 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 of/destroyed 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.

9.3.1 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The PI at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

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

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of study is defined as DBL. The database will be locked after all patients enrolled have either withdrawn from the study or completed at least 12 weeks of study drug since receiving the first dose, whichever comes first. After DBL, patients may continue to receive study drug as long as they are continuing to derive benefit from treatment as judged by the Investigator, do not have disease progression, or unmanageable drug-related toxicity. Patients continuing on study drug should be cared for according to local clinical practice.

Investigators must report SAEs directly to the AstraZeneca representative in accordance with Section 6.4.4, and continue to maintain study drug accountability as long as patients are receiving treatment with the study drug.

The study is expected to start in and to end by .

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 AZD6094.

10. DATA MANAGEMENT BY ASTRAZENECA OR REPRESENTATIVE

Data will be entered in the EDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests, and assessments specified in the protocol into the EDC system and according to the eCRF Instructions. The eCRF Instructions will also guide the study site in performing data entry. Data entered in the EDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified (SDV), reviewed/ queried and updated as needed. The PI is responsible for signing the eCRF and this can be delegated to a trained Investigator. The eCRF is signed electronically as per the eCRF instructions.

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 (e.g., IWRS etc) will be tested / validated as needed. The data collected through third party sources will be obtained and reconciled against study data.

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

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail. The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The study Data Management Plan will describe in greater detail the methods used to collect, check, and process clinical data. It will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

All decisions on the evaluability of the data from each individual patient must have been made and documented. Following DBL, required amendments to the database due to critical errors will only be allowed with the appropriate supporting documentation. Non-critical errors will not result in amendments to the database but will be captured via the appropriate documentation. The data will be frozen and then locked to prevent further editing. When all data have been coded, validated, signed and locked, clean file will be declared and the final database will be locked. Copy of the eCRF will be archived at the study site when the study has been closed.

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca. Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research will be reported separately from the CSR for the main study. Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR REPRESENTATIVE

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Tumour response rate

Patients will undergo regular tumour assessments until documented objective disease progression as defined by RECIST v1.1. At each visit the RECIST data for a patient will be assigned a response of CR, PR, SD, or PD depending on the status of the disease compared

with baseline and previous assessments. The response rate is defined as the number (%) of subjects with at least one visit response of CR or PR that is confirmed at least 4 weeks later. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of RR. This will be irrespective of whether or not subjects discontinued treatment or received a subsequent therapy prior to progression. The denominator for the RR rate will be the number of patients in the Full Analysis Set (FAS) for whom measureable disease is present at baseline.

In the case where a subject has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the subject will be defined as a responder. Similarly, if a subject has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10 mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions. A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.

In the case of stable disease, measurements should have met the stable disease criteria for a minumum interval of 5 weeks (6 weeks minus the 7-day visit window) following the start of treatment.

Progression of Target Lesions (TL) will be calculated in comparison with what the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, or SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

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

For TL measurements, if ≤1/3 of the TL sizes are missing (either not evaluable or not read, or the scan was not done) then a scaling up rule will be applied as follows:

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

- If >1/3 of lesions recorded at baseline are missing, then the target lesion response will be NE. However, if the sum of non-missing target lesion diameters would result in PD (i.e., if using a value of 0 for missing lesions the sum of diameters has still increased by >20% or more compared with the smallest sum of diameters on study and has an absolute increase ≥5 mm PD takes precedence over NE.
- A visit response of CR will not be allowed if any of the TL data are missing.

11.1.2 Progression-free survival

Progression-free survival is defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

If the subject progresses or dies after two or more missed visits, the subject will be censored at the time of the latest evaluable RECIST assessment. If the subject has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two visits of baseline.

Progression-free survival will be derived based on scan/assessment dates not visit dates. If RECIST assessments/scans contributing towards a particular visit are performed on different dates then the date of progression will be determined based on the earliest of the dates of the component that triggered the progression. With regard to censoring, a subject will be censored at the latest of the dates contributing to a particular overall visit assessment.

11.1.3 Duration of Response

Duration of response is defined as the time from the date of first documented response until the date of documented progression or any cause death. In the case where a subject does not progress following response, the duration of response will be the same as the PFS censoring time.

11.1.4 Change in tumour size

A secondary outcome variable for this study is percentage change from baseline in tumour size at 12 weeks. This is based on RECIST target lesion measurements taken at baseline and at week 12. Tumour size is the sum of the longest diameters of the target lesions. Target lesions are measureable tumour lesions. Baseline for RECIST is defined to be the last evaluable assessment prior to starting treatment. The percentage change in target lesion tumour size at week 12 will be obtained for each patient taking the difference between the sum of the target lesions at week 12 and the sum of the target lesions at baseline divided by the sum of the target lesions at baseline x 100 (i.e. [week 12 – baseline]/baseline x 100).

Patients who progress before week 12 should have had a tumour assessment performed at the time of progression prior to treatment discontinuation. The tumour size from their latest

progression assessment will be used instead of the week 12 assessment for these patients. In addition best percentage change in target lesion tumour size from baseline will be assessed where best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction at any point in the study.

11.1.5 Overall Survival

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

11.2 Calculation or derivation of safety variable(s)

11.2.1 Exposure to investigational product

Total time on study treatment (AZD6094), as well as total exposure to study treatment and the amount delivered relative to the intended amount will be summarised. The number of patients with pauses and reductions and AZD6094 relative dose intensity (RDI) and percentage intended dose (PID) will also be summarised. The RDI is the percentage of the actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation. PID is the percentage of the actual dose delivered relative to the intended dose through progression.

11.2.2 Adverse events, laboratory changes, vital signs and ECGs

Safety profiles will be assessed in terms of AEs and laboratory data, vital signs and ECGs that will be collected for all patients.

QTc will be calculated by AstraZeneca using both Bazett's and Fridericia's formulae.

11.2.3 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert or designee will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician or designee, be considered OAEs and reported as such in the CSR. A similar review of laboratory data will be performed for identification of OAEs.

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

11.3 Calculation or derivation of pharmacokinetic variables

The PK analyses will be performed at AstraZeneca R&D. The actual sampling times will be used in the PK calculations. PK parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined:

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal plasma half-life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to infinity (AUC), oral plasma clearance (CL/F), oral volume of distribution during terminal phase (V_z/F), mean residence time (MRT).

11.3.1 Urine pharmacokinetic parameters

The renal clearance (CL_R) will be calculated as the cumulative amount of AZD6094 excreted unchanged in the urine (Ae) divided by the appropriate AUC. Ae will be presented as a percentage of the dose i.e., (Ae/dose) · 100.

11.4 Calculation or derivation of pharmacodynamic variable(s)

Change in expression of tumour phospho-cMet and total-cMet from baseline will be reported in the CSR.

Results from the exploratory tumour and blood biomarker research may be reported separately from the CSR for the main study.

The PK, PDc, demographic, safety and efficacy data collected in this study may also be combined with similar data from other studies and explored using PK and PK/PDc population analysis methods. A population PK, PK/PDc analysis plan and the results of any analysis may be reported separately from the CSR.

11.5 Calculation or derivation of pharmacogenetic variables

Pharmacogenetic research from blood samples collected as part of this study will be reported outside of the CSR.

11.6 Calculation or derivation of health economic variables

Results from the health economic data (health state utility and hospital resource use) may be reported separately from the Clinical Study Report for the main study.

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

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

The Full Analysis Set (FAS) will be utilised for efficacy evaluations and will consist of all enrolled subjects with centrally confirmed PRCC and measureable disease at baseline who receive at least one dose of AZD6094.

12.1.2 Safety analysis set

All subjects who received at least one dose of AZD6094 will be included in the safety set.

12.1.3 Stage 1 efficacy analysis set

The Stage 1 efficacy analysis set will consist of the first 20 patients in the FAS.

12.2 Methods of statistical analyses

The statistical analyses will be performed by under the direction of the Biometrics Group, AstraZeneca.

All safety, tolerability, efficacy, PK, and PDc data will be summarised and listed.

The methods of statistical analyses described below will be performed at the end of Stage 1 and at the end of the study on the data of both Stages 1 and 2 combined.

Additional sub-group analyses, stratified by untreated or previously treated, may be performed if patient numbers are sufficient.

12.2.1 Demographic data

Characteristics of patients, including medical history and disease characteristics at baseline will be listed for each patient and summarised as part of the study. This will include assessment of risk criteria in accordance with the MSKCC risk category prognostic model in advanced renal cell cancer (Motzer et al 2002). Patients risk category will be classified as:

Favourable risk – 0 risk factors
Intermediate risk – 1 or 2 risk factors
Poor risk – 3 or more risk factors

Risk factors include: Karnofsky Performance Status less than 80%, time from diagnosis to salvage treatment of less than 1 year, hemoglobin below the lower limit of normal, corrected serum calcium greater than the upper limit of normal, serum LDH greater than 1.5 times ULN.

12.2.2 Exposure

Exposure to investigational product, i.e., total amount of study drug received, will be listed and summarised for all patients. Total exposure, time on study drug, and dose intensity (RDI and PID) will be summarised, along with the number and percentage of patients with at least one dose interruption and least one dose reduction. Reasons for discontinuation of investigational product will be listed including the study day of treatment discontinuation and will be summarised by dose group.

12.2.3 Efficacy

12.2.3.1 Response rates

Proportion of patients (combined Stages 1 & 2) achieving a confirmed objective response (CR or PR) will be presented with a two-sided 95% CIs using Clopper-Pearson method (Clopper and Pearson, 1934). The number and percentage of patients in each response category (CR, PR, SD, PD, NE) will be summarised. Results may be summarized by the MSKCC risk category if patient numbers permit.

12.2.3.2 Duration of response

Kaplan-Meier plots of duration of response in the responding patients will be produced and appropriate summary statistics will be presented (number of responses, number of responses that have progressed, median, quartile, minimum and maximum duration of response using the Kaplan-Meier estimate).

12.2.3.3 Change in tumour size

The absolute values, change in target lesion tumour size from baseline and percentage change in target lesion tumour size from baseline will be summarised using descriptive statistics and presented at each time point.

The best change in target lesion tumour size from baseline, (where best change in target lesions size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction) will also be summarised.

The number and percentage of subjects in each treatment group whose week 12 data is imputed will also be presented.

Waterfall plots (bar charts) indicating the week 12 and the best percentage change from baseline in sum of the diameters of TLs will be produced. Reference lines at the +20% and -30% change in tumour size levels will be added to the plots, which correspond with the definitions of progression and 'complete or partial' response respectively. In these waterfall plots, the subjects whose week 12 percentage change in tumour size is based on an imputation, due to missing target lesions data, will be clearly identified.

12.2.3.4 Progression-free survival

Exploratory summaries (number of events, medians, proportion progression free at 6 months and 12 months) and Kaplan Meier plots will be provided. Results may be summarized by the MSKCC risk category if patient numbers permit.

12.2.3.5 Overall Survival

Exploratory summaries (number of deaths, medians, proportion alive at 1 year and 2 years) and Kaplan Meier plots will be provided. Results may be summarized by the MSKCC risk category if patient numbers permit.

12.2.4 Pharmacokinetics

Plasma concentrations of AZD6094, M2 and M3 will be summarised by nominal sample time. Plasma concentrations at each time point will be summarised according to dose by the following summary statistics:

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

The following summary statistics will be presented for AUC, $AUC_{(0-24)}$, $AUC_{(0-t)}$, AUC_{ss}, C_{max}, $C_{ss\ max}$, and $C_{ss\ min}$:

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

The following summary statistics will be presented for CL/F, CL_{ss}/F, volume of distribution, $t_{½\lambda z}$, Rac, time dependency:

- Arithmetic mean

- Standard deviation
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for t_{max} and $t_{max\ ss}$:

- Median
- Minimum
- Maximum
- Number of observations

The pharmacokinetic data for AZD6094, M2 and M3 at steady state will also be displayed graphically. Displays will include plasma concentration patient profiles (on the linear and log scale) versus time and g_{mean} concentration (± standard deviation) versus time, stratified by dose.

12.2.5 Pharmacodynamics

The pharmacodynamic effects of AZD6094 will be evaluated in tumour tissue paired biopsies (a pre-dose tumour biopsy and paired tumour biopsies post-dose). The biomarkers investigated may include, but are not limited to phospho-cMet and total-cMet. The technological platform for the pharmacodynamic analysis will be immunohistochemistry, but may not be limited to this.

12.2.6 Exploratory research

Results from the exploratory biomarker and pharmacogenetic research, PROs and health economic data may be reported separately from the Clinical Study Report for the main study.

Biomarker research and pharmacogenetics

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

Patient reported outcomes

Analyses on the FACT-G, FKSI-19 and EQ-5D-5L will be based on the instruments' scoring manuals.

Hospital Resource Use

Descriptive statistics relating to the frequency of hospital resource use items, including hospital admission, type of contact (hospitalisation, outpatient, day case), reason, length of stay (including ICU) and procedures undertaken will be derived from the resource use information.

12.2.7 Safety analysis

Safety data will not be analysed formally. Standard data summaries will be produced for safety data including (but not limited to):

- Summaries of AEs of any CTCAE grade – summarised by MedDRA preferred term and system organ class and CTCAE grade
- Summaries of Grade 3 and above AEs
- SAEs
- AEs occurring before the first dose of investigational product will be listed only and not included in the summaries
- Any AE occurring within the defined 30 day follow up period after discontinuation of investigational product will be included in the AE summaries. AEs occurring after the 30 days follow up period will be listed only, not summarised.
- Deaths will be summarised by primary cause, along with AEs with an outcome of "fatal"
- Haematology, clinical chemistry, vital signs, ECG data and concomitant medication will be listed individually by patient and will be suitably summarised
- Any qualitative safety assessments for urinalysis will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration, or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared with baseline.

12.2.8 Stage 1 data review analysis

This is an open label study with a primary endpoint of objective response (confirmed PR or CR) as assessed by the Investigator.

The proportion of patients (Stage 1) achieving a confirmed objective response (CR or PR) will be presented with a one-sided 80% CI and a two-sided 95% CIs using Clopper-Pearson method. The number and percentage of patients in each response category (CR, PR, SD, PD, NE) will be summarised.

Other safety, tolerability, efficacy, PK, and PDc data will be summarised and listed, as above, as appropriate.

12.2.9 End of study analysis

If the study will pass the futility analysis at the end of Stage 1, then at the end of the study analysis will be performed on the total data from the patients in both Stages 1 and 2 combined.

At the end of the study the primary end-point (ORR) will be tested against the null H_0: ORR≤25% at the one-sided significance level of α=0.025 in two populations as co-primary objectives: the total population of confirmed PRCC patients and the subgroup of MET positive PRCC patients. Overall FWER will be controlled at the one-sided level α=0.025 using the Hochberg procedure. Specifically, if the ORR will be tested with p-value < α in both populations simultaneously, then the null will be rejected in both populations. Otherwise, if the p-value of the test in one of the populations will be smaller than $\alpha/2$ then the null will be rejected in that population. If neither of these conditions will be met then the null will be accepted for both tested populations.

12.3 Determination of sample size

The study will comprise two stages. In Stage 1 approximately 20 patients will be enrolled. This group is considered sufficient to provide preliminary assessment of the anti-tumour activity of AZD6094 in the form of non-binding futility analysis. In studies in which PRCC patients were treated with sunitinib the typical response rates were around 10%. This response rate informs the decision about futility and the observed response rate in Stage 1 of this study must at least match 10%, i.e. ORR>2 of 20 evaluable patients to proceed to Stage 2.

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

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The PI is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, (see Section 6.4.4). In the case of a medical emergency the Investigator may contact the International Study Chair. If the Study Chair is not available, contact the Medical Monitor at or the Senior Director.**

Name	Role in the study	Address & telephone number

13.2 Overdose

There are no data on overdosing with AZD6094 thus far from the first-time-in-man study. There is no definition of what constitutes an overdose. There is no known antidote.

Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

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

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

Safety Department works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

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

13.3 Pregnancy

All outcomes of pregnancy should be reported to Safety Department.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study, AZD6094 should be discontinued immediately.

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

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

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

The same timelines apply when outcome information is available.

13.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose of AZD6094.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

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