A-PREDICT

A Phase II Study of Axitinib in Patients with Metastatic Renal Cell Cancer Unsuitable for Nephrectomy

Chief Investigator	James Larkin
Sponsor:	The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust
Approval:	Cancer Research UK
Funder:	Pfizer
Coordinating Trials Unit:	ICR Clinical Trials and Statistics Unit (ICR-CTSU) The Institute of Cancer Research

PROTOCOL Version 9

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The A-PREDICT trial has been approved
by Cancer Research UK's Clinical Trials Awards & Advisory Committee (CTAAC)
The A-PREDICT trial is part of the National Institute for
Health Research Clinical Research Network Trial Portfolio

ADMINISTRATION

Scientific Coordination

Prof James Larkin
Chief Clinical Investigator
Consultant Medical Oncologist,
Royal Marsden Hospital
Fulham Road
London
SW3 6JJ
Tel +44 20 7808 2132
Fax +44 20 7808 2688
Email: James.Larkin@rmh.nhs.uk

Prof Charles Swanton
Chief Scientific Investigator
The Francis Crick Institute
1 Midland Road
London NW1 1AT
Tel +44 20 7269 3463
Fax +44 20 7269 3094
Email: Charles.Swanton@cancer.org.uk

Trial Coordination

A-PREDICT Trial Manager
ICR Clinical Trials & Statistics Unit (ICR-CTSU)
Division of Clinical Studies
The Institute of Cancer Research
Sir Richard Doll Building
Cotswold Road
Sutton, Surrey SM2 5NG

ICR-CTSU (a UKCRC registered NCRI cancer trials unit) is responsible for the day to day conduct of the trial.

ICR-CTSU Scientific Lead : Judith Bliss
Tel: 020 8722 4297
Judith.Bliss@icr.ac.uk

ICR-CTSU Senior Statistician: Lucy Kilburn
Tel: 020 8722 4080
apredict-icrctsu@icr.ac.uk

ICR-CTSU Clinical Trials Programme Manager:
Rebecca Lewis
Tel: 0208 722 4081
apredict-icrctsu@icr.ac.uk

A-PREDICT Trial Manager: Steven Penegar
Tel: 0208 722 4238
apredict-icrctsu@icr.ac.uk

Any questions relating to this protocol should be addressed in the first instance to the A-PREDICT Trial Manager within ICR-CTSU:

Email: apredict-icrctsu@icr.ac.uk

General enquiries: 0208 722 4238

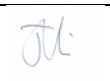
Fax: 0208 770 7876

PROTOCOL DEVELOPMENT GROUP

Prof. Judith Bliss	Director, ICR-CTSU,	ICR-CTSU, The Institute of Cancer Research,
Dr James Larkin	Consultant Medical Oncologist	Royal Marsden Hospital
Prof. Charles Swanton	Consultant Medical Oncologist	The Francis Crick Institute
Dr Ekaterini Boleti	Consultant Medical Oncologist,	Royal Free Hampstead NHS Trust
Prof. Martin Gore	Consultant Medical Oncologist,	Royal Marsden Hospital
Prof. Robert Hawkins	Director of Medical Oncology	University of Manchester/Christie Hospital
Dr Agnieszka Michael	Consultant Medical Oncologist	Royal Surrey County Hospital
Dr Tom Powles	Consultant Medical Oncologist	St Bartholomew's & The Royal London Hospital
Dr Simon Chowdhury	Consultant Medical Oncologist	Guy's and St Thomas' Hospital
Dr Lisa Pickering	Consultant Medical Oncologist	Royal Marsden Hospital
Dr Rosalie Fisher	Clinical Research Fellow	Royal Marsden Hospital
Mr Tim O'Brien	Consultant Urologist	Guy's and St Thomas' Hospital
Dr Aslam Sohaib	Consultant Radiologist	Royal Marsden Hospital
Claire Snowdon	Deputy Director (Operations)	ICR-CTSU, The Institute of Cancer Research,
Lucy Kilburn	Senior Statistician	ICR-CTSU, The Institute of Cancer Research,
Rebecca Lewis	Senior Trials Manager	ICR-CTSU, The Institute of Cancer Research,
Eleftheria Kalaitzaki	Translational Statistician	ICR-CTSU, The Institute of Cancer Research,
Andrew Rowan	Principal Scientific Officer	The Francis Crick Institute

The Trial Management Group (TMG) will be constituted from members of the Protocol Development Group and Principal Investigators from a subset of participating centres. A copy of the current membership of the TMG can be obtained from the A-PREDICT Trial Manager at ICR-CTSU.

Protocol Authorised by:

Name & Role	Signature	Date
Dr James Larkin (Chief Clinical Investigator)		02/062020

This protocol describes the A-PREDICT trial and provides information about procedures for entering patients. The protocol should not be used as a guide for the treatment of other patients. Every care has been taken in the preparation of this protocol, but corrections or amendments may be necessary. These will be circulated, once approved, to investigators in the trial. New potential centres are advised to contact ICR-CTSU to confirm they have the most recent version of the protocol.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) as amended. It will be conducted in compliance with the protocol, the Data Protection Act (Z6364106) and other regulatory requirements as appropriate.

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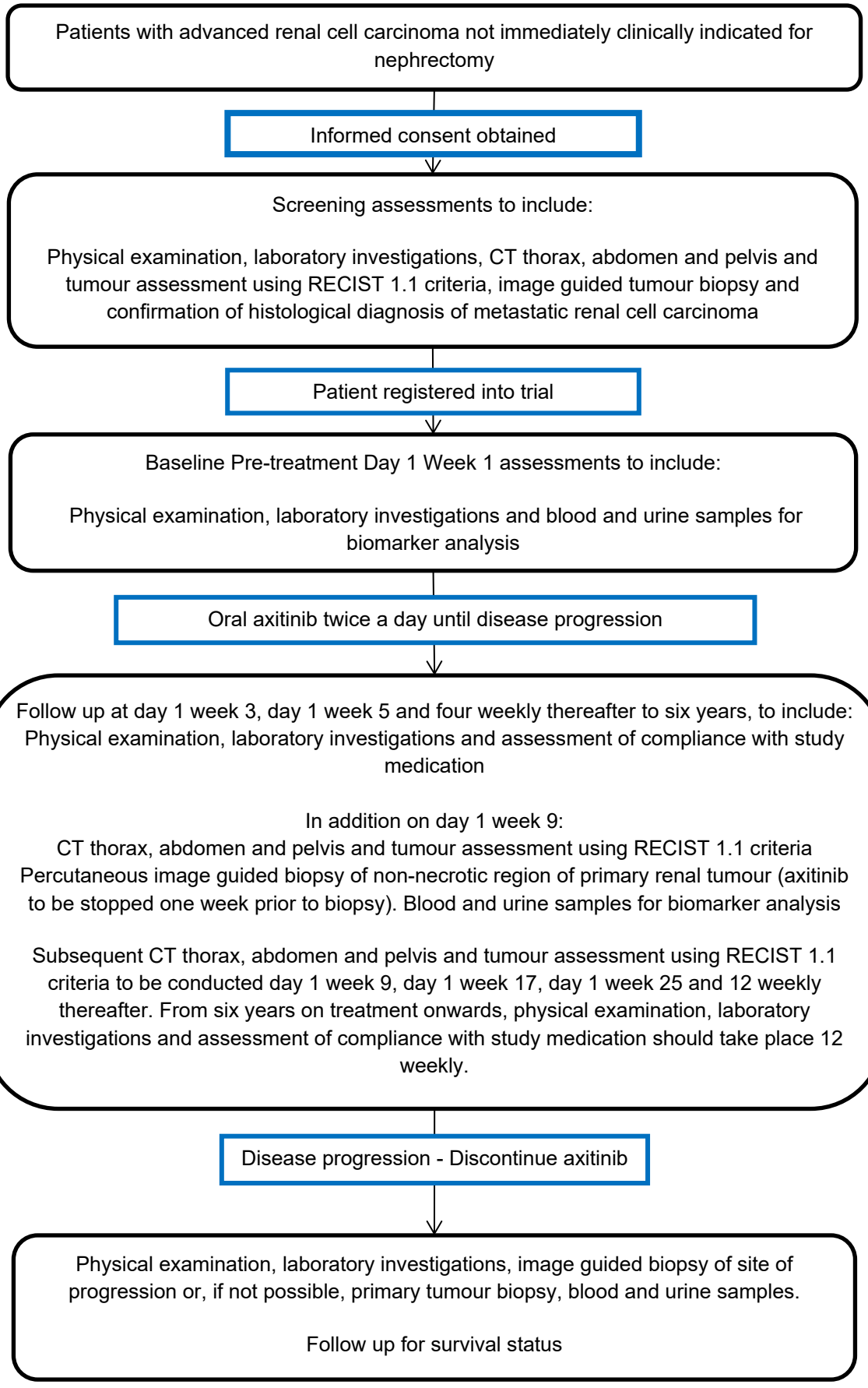
TRIAL SUMMARY

PRODUCT	Axitinib
PROTOCOL NUMBER	ICR-CTSU/2011/10033
PROTOCOL TITLE	A-PREDICT: A Phase II Study Of Axitinib In Metastatic Renal Cell Cancer in Patients Unsuitable for Nephrectomy
TARGET DISEASE	Metastatic renal cell carcinoma (mRCC)
STUDY SITE	UK wide
PATIENT POPULATION	Patients (n=99) with metastatic renal cell carcinoma of predominant clear cell histology who are not immediately clinically indicated for cytoreductive nephrectomy
STUDY OBJECTIVES	To evaluate efficacy, safety, toxicity and changes in biomarkers during therapy with axitinib
STUDY DESIGN	Single arm, open label, phase II, multicentre trial
TREATMENT REGIMEN	Oral axitinib twice a day. 5mg starting dose escalated to maximum of 10mg until disease progression
PRIMARY ENDPOINT	Freedom from progression at 6 months
SECONDARY ENDPOINTS	Safety, toxicity, changes in biomarkers, response rate, progression free and overall survival
FOLLOW UP	Day 1 of week 1, 3 and 5 and four weekly to six years with tumour staging on day 1 of of week 9, 17, 25 and 12 weekly thereafter. After six years on treatment patients will be followed up every 12 weeks. All patients will be followed up until death or withdrawal of consent for further follow up.

TRANSLATIONAL STUDY SAMPLE COLLECTION	**Pre-registration (up to 14 days prior to commencing treatment)** Percutaneous image guided biopsy of non-necrotic region of primary renal tumour (and one metastatic site if possible). **Baseline – pre-treatment day 1 week 1** • Two blood samples • Urine sample **Day 1 week 9** • Percutaneous image guided biopsy of non-necrotic region of primary renal tumour – axitinib to be stopped one week prior to biopsy • Two blood samples • Urine sample **At disease progression** • Image guided biopsy of site of progression or, if not possible, percutaneous primary renal tumour biopsy, one week after stopping axitinib and prior to commencement of any subsequent treatment • Two blood samples • Urine sample

TRIAL SCHEMA



1. INTRODUCTION

Renal cell carcinoma (RCC) is diagnosed in around 8,500 patients and accounts for approximately 3% of malignant disease annually in the UK [1]. Many patients initially present with advanced or unresectable disease and up to 30% of patients treated by nephrectomy with curative intent for localised disease will relapse [2]. The 5-year survival rate for metastatic RCC (mRCC) is less than 10%. Historically the prognosis for metastatic RCC was poor with a median survival of 6-8 months [3] and reported response rates to chemotherapy [4] and hormonal agents [5] have been of the order of only 5-10%. Approximately half of RCC tumours have mutations in the Von Hippel-Lindau gene (VHL). VHL loss increases expression of the hypoxia-inducible factor alpha transcription factors (HIF-1α and HIF-2α). These factors regulate the expression of vascular endothelial growth factor (VEGF) and other molecules implicated in angiogenesis and invasion. These pathways are important in the pathophysiology of RCC although their roles are not fully understood.

1.1. SURGICAL TREATMENT OF METASTATIC RENAL CELL CARCINOMA

Nephrectomy is the mainstay of curative treatment for renal cell carcinoma and has also been shown to be of palliative benefit in metastatic disease. Two phase III trials, European Organization Research and Treatment of Cancer 30947 [6] and SouthWest Oncology Group 8949 [7], have demonstrated a survival benefit for nephrectomy followed by interferon versus interferon alone in patients with histologically confirmed progressive renal cell carcinoma and good performance status at presentation. Nephrectomy is generally a relatively safe and well-tolerated operation in experienced hands: a report from Memorial Sloan Kettering Cancer Centre (MSKCC) of 692 radical nephrectomies for renal cell cancer performed between 1995 and 2002 quotes a 3% procedure-related complication rate and 0.2% procedure-related mortality [8].

1.2. MEDICAL TREATMENT OF METASTATIC RENAL CELL CARCINOMA

Metastatic clear cell renal carcinoma generally is resistant to chemotherapy. Cytokine-based therapies have been used in the treatment of metastatic RCC but with limited anti-tumour effect. For example, interferon-α (IFN-α) has a response rate of approximately 10–15% in appropriately selected individuals with favourable or intermediate risk as per the MSKCC scoring system [9, 10].

Randomised trials reported in the last 5 years have demonstrated that a number of agents such as the monoclonal antibody bevacizumab [11, 12] and the kinase inhibitors everolimus [13], sorafenib [14], pazopanib [15], sunitinib [16] and temsirolimus [17] are active in advanced RCC. Bevacizumab is directed against VEGF, a key mediator of angiogenesis, whilst sorafenib, pazopanib and sunitinib inhibit a number of targets including the VEGF and platelet-derived growth factor (PDGFR) receptor tyrosine kinases. Everolimus and temsirolimus inhibit the intracellular mammalian target of rapamycin (mTOR) kinase. Sunitinib [16] and temsirolimus [17] have demonstrated efficacy in comparison with immunotherapy in the 1st line setting in patients with favourable and poor risk advanced disease respectively. Sorafenib has demonstrated efficacy in comparison with placebo in the 2nd line setting in patients with immunotherapy-refractory disease [14]. Everolimus is active in patients that have progressed despite therapy with sorafenib or sunitinib [13].

1.3. PATIENTS PRESENTING WITH METASTATIC DISEASE NOT CLINICALLY INDICATED FOR NEPHRECTOMY

A significant number of patients presenting with metastatic disease are not treated with palliative nephrectomy. There are a number of reasons for this including comorbidity, technically inoperable disease, the presence of a significant volume of metastatic disease, the presence of metastatic disease in multiple or particular sites (e.g. liver) and the presence of other poor risk factors e.g. serum LDH>ULN, hypercalcaemia, anaemia and poor performance status (PS). Outcomes are generally extremely poor in this group. The strongest evidence base for systemic treatment in this group is for the mTOR inhibitor temsirolimus, a drug not approved by the National Institute for Health and Clinical Excellence (NICE) for use in the UK. In a phase III study [17] patients with at least 3 of 6 poor risk factors (time from diagnosis of metastatic disease to

therapy <12 months, 2 or more organ sites of metastatic disease, poor PS, raised LDH, hypercalcaemia or anaemia) were randomized to interferon, temsirolimus or the combination of the drugs. Approximately a third of patients had not undergone prior nephrectomy. Outcomes were best in the temsirolimus only group, compared to the interferon and combination groups, with a median progression-free survival (PFS) of 5.5 months and median overall survival (OS) of 10.9 months; as a consequence, temsirolimus is the preferred treatment choice in this group. Patients in this group in the UK may be offered either sunitinib (despite the fact that the evidence base for its use in this group is limited) or best supportive care alone. There is a clear need for improved outcomes in this group of patients and to identify mechanisms of sensitivity and resistance to VEGF-targeted therapy.

1.4. AXITINIB

Axitinib is a potent oral VEGFR2 and 3 inhibitor at picomolar concentrations and VEGFR1, PDGFRs and c-KIT inhibitor at low nanomolar concentrations. In phase II clinical trials, axitinib has shown efficacy in sorafenib and cytokine refractory mRCC patients. A recently reported phase III trial, showed superiority over sorafenib as second line therapy [18], leading to the licensing of axitinib in this indication by the US Food and Drug Administration (FDA) agency in January 2012. Axitinib was subsequently licensed for the same indication by the European Medicines Agency. Furthermore, the efficacy of axitinib is under evaluation in other tumour types, and has shown activity in lung [19], thyroid [20], and pancreatic [21] cancers, and melanoma [22].

1.4.1. PRECLINICAL DATA

In vitro, axitinib inhibits cellular phosphorylation of VEGFR2 and 3 with an IC50 of about 0.2 nmol/L. It has a higher IC50 for VEGFR1 (1.2 nmol/L), PDGFR-β (1.6 nmol/L), PDGFR-α (5 nmol/L) and c-KIT (1.7 nmol/L). It reduces phosphorylation of downstream signalling molecules mediated by VEGF in a rapid and dose-dependent manner, including Akt, endothelial nitric oxide synthase and extracellular signal regulated kinase (ERK).

In mouse xenografts, twice daily oral axitinib inhibited the primary tumour and controlled metastases in human melanoma (M24mwt), colorectal cancer (HCT-116) and RCC (SN12C) models. Within axitinib treated tumours, there was reduced CD31 and Ki-67 staining and increased caspase-3 staining. Microscopic examination of tumour vasculature in preclinical models of pancreatic islet cell tumours and Lewis lung carcinomas has shown that axitinib reduces patency and flow. Axitinib has the greatest effects on endothelial cells and fenestrated vessels, resulting in normalisation of the surviving tumour vasculature.

1.5. HUMAN STUDIES OF AXITINIB

1.5.1. EFFICACY - PHASE I

In an initial phase I study, 3 of 36 patients had partial responses determined by Response Evaluation Criteria in Solid Tumours (RECIST) including 2 patients with RCC and 1 patient with adenoid cystic carcinoma [23]. In a Japanese phase I trial, none of 12 recruited patients had a partial response but 3 patients had stable disease at 24 weeks, seen in one patient each with colorectal carcinoma, thymic cancer and non-small cell lung cancer (NSCLC) [24].

1.5.2. EFFICACY - PHASE II: AXITINIB IN CYTOKINE-REFRACTORY METASTATIC RCC

In a single arm, open label, phase II trial in cytokine-refractory mRCC, axitinib was administered at a starting dose of 5mg twice daily in the fasted state as 28 day treatment cycles until disease progression or significant toxicity [25]. Fifty-two patients were recruited with a median age of 59 years and performance status 0 or 1. Forty-nine patients (95%) had previously undergone a nephrectomy and none of the patients had previously received TKIs. All patients had clear cell histology, except one patient who had papillary carcinoma.

The objective response rate (ORR) was 44.2% (95% CI: 30.5-58.7%); there were 2 complete and 21 partial responses. Twenty-two patients had stable disease for at least 8 weeks, including the patient with papillary carcinoma. Four patients had early progression and 3 patients could not be assessed for response. The median TTP was 15.7 months and median overall survival was 29.9 months. The median duration of axitinib therapy was 9.4 months and median dose was 8.83 mg/day, as 15 patients had dose reductions for adverse events including fatigue, hypertension and diarrhoea. Axitinib was discontinued due to adverse events in ten patients. The most frequent grade 1-4 axitinib related adverse events were diarrhoea, hypertension, fatigue, nausea and hoarseness. The most common grade 3-4 adverse events were hypertension (15.4%), diarrhoea (9.6%) and fatigue (7.7%). Thirty patients had axitinib induced hypertension, eight of whom had grade 3-4 hypertension. Hypertension was resistant to anti-hypertensive therapy in 8 patients, seven of whom had hypertension at baseline. There were no detectable haematological toxicities. Four patients had treatment related proteinuria which resolved once axitinib was stopped.

1.5.3.EFFICACY - PHASE II: AXITINIB IN SORAFENIB REFRACTORY METASTATIC RCC

In a single arm, open label, phase II study, patients with sorafenib refractory mRCC received a starting dose of axitinib 5mg twice daily with food until disease progression or unmanageable toxicity [26]. Sixty-two patients were recruited; all had undergone prior nephrectomy and 59 patients had clear cell /mixed histology. Median age was 60 years and all patients were PS 0 or 1. The most common prior therapies in addition to sorafenib were sunitinib and cytokine therapy, received by 14 (22.6%) and 38 (61.3%) patients, respectively.

The ORR was 22.6% (95% CI 12.9-35.0%), with 14 patients experiencing a partial response and no complete responses. Tumour responses were observed in patients who received 5 mg twice daily or higher, and also in patients whose dose was reduced to below 5 mg twice daily. Patients who had a partial response received doses ranging from <4mg to 9-10mg twice daily. Eleven patients (17.8%) had stable disease. The median progression-free survival (PFS) was 7.4 months (95% CI 6.7-11.0 months) and median OS was 13.6 months (95% CI 8.4-18.8 months).

The most common grade 3-4 adverse events included hypertension (16.1%), fatigue (16.1%), hand-foot syndrome (16.1%), dyspnoea (14.5%) and diarrhoea (14.5%). Twelve patients stopped axitinib due to treatment related adverse events. Two patients developed congestive heart failure, both of whom had a history of cardiovascular disease, and two patients had cerebral haemorrhages during the study. One of the latter patients was subsequently diagnosed with a cerebral metastasis at the site of haemorrhage. Most haematological toxicities were mild or moderate (grade 1 or 2) except grade 3 lymphopaenia experienced by 9 of 55 evaluable patients (16.4%).

1.5.4.SAFETY AND TOLERABILITY - PHASE I

The primary dose limiting toxicity in the initial phase I trial was hypertension[23]; in most cases it responded to anti-hypertensive therapy and resolved after axitinib was stopped. The incidence and severity of hypertension was dose-dependent, all patients with axitinib-induced hypertension at dose 5mg twice daily were managed with standard anti-hypertensives. Prior to blood pressure monitoring two patients had uncomplicated seizures in the absence of brain metastases at doses 10mg and 20mg twice daily, these may have been related to hypertensive crises.

Three bleeding events were reported during the phase I study. A patient with central NSCLC had a fatal haemoptysis attributed to axitinib. A patient with peripheral NSCLC had grade 1 haemoptysis while taking axitinib which was subsequently stopped. Two weeks later the patient had grade 4 haemoptysis and died, this patient's death was reported as secondary to disease progression and concurrent infection. Finally, there was 1 episode of grade 1 rectal bleeding.

Asymptomatic proteinuria was detected in seven of the first ten patients. Consequently, patients with proteinuria >0.5gram/24 hours were not recruited and treatment reviews were required for all patients with proteinuria ≥1gram/24 hours. These amendments reduced the incidence and severity of proteinuria.

Thrombocytopenia was the only haematological toxicity in the phase I trial, with grade 2 thrombocytopenia affecting one patient taking 20mg twice daily.

1.5.5.SAFETY AND TOLERABILITY - PHASE II

The commonest non-haematological adverse events grade 1-4 reported in phase II axitinib monotherapy trials were hypertension, fatigue, diarrhoea, anorexia, nausea and hoarseness. The main grade 3-4 adverse events were similar, except hand-foot syndrome and proteinuria were also reported. Most adverse events were manageable. Hypertension usually responded to anti-hypertensive therapy and resolved once axitinib was stopped.

The starting dose in all but one of the phase 2 studies conducted to date was 5mg twice daily of axitinib. In one metastatic breast cancer study, axitinib dose was titrated up from a starting dose of 5mg twice daily in 1–3mg increments in patients tolerating axitinib. Those subjects who could tolerate axitinib with no adverse events related to axitinib above CTCAE grade 2 for consecutive 2 week periods were permitted to increase their dose step-wise to 7mg twice daily and then to 10mg twice daily, unless their BP was >150/90mm Hg or the subject was receiving antihypertensive medication. All studies ongoing at the time of writing allow axitinib dose reductions to as low as 2mg twice daily for treatment-related adverse events. Except for an increase in hand-foot syndrome and slight increase in the incidence of hypertension, it appears that patients whose dose is titrated to between 6-10mg twice daily doses do not experience increased toxicities if they have previously tolerated 5mg twice daily starting dose. Axitinib dose titration will be permitted within A-PREDICT, consistent with previous clinical trial protocols and the drug development programme for axitinib.

1.6. A-PREDICT STUDY RATIONALE

Patients presenting with metastatic RCC not immediately clinically indicated for nephrectomy constitute a very poor prognosis group with limited treatment options. The strongest evidence base for systemic therapy in this group is for the mTOR inhibitor temsirolimus but a potent VEGFR kinase inhibitor has never been prospectively evaluated.

Axitinib is well tolerated and has demonstrated a high response rate in metastatic RCC but the mechanisms of sensitivity and resistance to treatment in vivo remain to be established. A clinical trial of axitinib in patients with metastatic RCC where immediate cytoreductive nephrectomy is not suitable offers an opportunity to evaluate a potent VEGFR kinase inhibitor in this setting. Furthermore, pre-treatment and on treatment biopsies will be obtained and compared using the functional genomics approach developed by the PREDICT Consortium[27]. Targets for axitinib in RCC in vivo can thereby be identified and changes in biomarkers correlated with both response to treatment and toxicity. If significant activity is seen in the primary lesion then there may be a role for axitinib in the primary medical therapy of locally advanced renal cell carcinoma.

2. TRIAL OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary clinical objective of this study is to define the activity of axitinib given to patients with metastatic renal cell carcinoma where cytoreductive nephrectomy is not immediately clinically indicated.

2.2. SECONDARY OBJECTIVES

The secondary objectives of this study are to determine toxicity, response to treatment, proportion of patients that become suitable for nephrectomy, progression free and overall survival.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives of this study are to:

- correlate changes in biomarkers with toxicity, response to treatment and survival.

- investigate any effect of treatment on the extent of inferior vena cava (IVC) venous tumour thrombus (VTT)

3. TRIAL DESIGN

A-PREDICT is a single arm, single agent, open label, multicentre, phase II study of axitinib in patients with metastatic renal cell carcinoma of predominant clear cell histology and not immediately clinically indicated for debulking nephrectomy (as judged by the treating clinician).

Patients who have provided consent and have satisfied the eligibility criteria will be registered into the trial. The starting dose of axitinib will be 5 mg twice daily by mouth, escalating to a maximum of 10mg twice daily by mouth according to tolerability of treatment, for as long as patients are deriving clinical benefit. Treatment will be paused for one week prior to the week 9 biopsy. Disease progression will be evaluated according to RECIST v1.1 criteria 8 weeks after commencing treatment, at 8 weekly intervals to 6 months and 3 monthly thereafter. Blood and tumour tissue samples will be taken prior to and during therapy to evaluate biomarkers of treatment response. Nephrectomy will be carried out on any patient who becomes suitable in the opinion of the treating clinician during the course of the trial. Where possible, tissue samples will be taken from resected specimens. Response to axitinib in marker lesions will be correlated with changes in biomarkers.

4. STUDY ENDPOINTS

4.1. PRIMARY ENDPOINT

- The proportion of patients treated with axitinib who are free from disease progression 6 months from the commencement of treatment according to RECIST v1.1 criteria [28]

4.2. SECONDARY ENDPOINTS

- Best overall response
- Progression free survival
- Overall survival
- Safety and toxicity of axitinib (by NCI CTC grading version 4 [29])
- Number of patients who become suitable for nephrectomy as a consequence of therapy with axitinib

4.3. EXPLORATORY ENDPOINTS

- Molecular and pathological changes in biomarkers as a consequence of axitinib therapy
- Effect of axitinib therapy on extent of venous tumour thrombus in the inferior vena cava

5. PATIENT SELECTION & ELIGIBILITY

5.1. NUMBER OF PATIENTS

The aim is to recruit 99 participants.

5.2. SOURCE OF PATIENTS

Potential participants are those for whom an immediate cytoreductive nephrectomy is not clinically indicated. This may include patients with unresectable primary tumours, those with a large metastatic burden or those unfit for nephrectomy. Participants will be identified in oncology clinics and discussed at Multi-Disciplinary Team (MDT) meetings.

5.3. INCLUSION CRITERIA

1. Histologically confirmed metastatic renal cell carcinoma of predominant clear cell histology
2. Not immediately clinically indicated for cytoreductive nephrectomy as judged by treating clinician(s)
3. Not suitable for 'watch and wait' policy as determined by treating clinician(s)
4. No prior systemic therapy for renal cell carcinoma
5. Measurable metastatic disease using RECIST v1.1 (see Appendix A)
6. 18 years of age or older
7. Life expectancy of 12 weeks or greater
8. ECOG performance status 0 or 1
9. Adequate organ function as defined by serum aspartate transaminase (AST) or serum alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN), or AST or ALT ≤5 x ULN if liver function abnormalities are due to liver metastases; total serum bilirubin ≤1.5 x ULN
10. Adequate haematological function as defined by absolute neutrophil count (ANC) ≥1500/μL, platelets ≥75,000/μL, haemoglobin ≥9.0 g/dL and prothrombin time (PT) ≤1.5 x ULN
11. Serum creatinine ≤1.5 x ULN or calculated creatinine clearance ≥ 60 mL/min;
12. Urinary protein <2+ by urine dipstick. If dipstick is ≥2+ then a 24-hour urine collection can be done and the patient may enter only if urinary protein is <2g per 24 hours.
13. No evidence of pre-existing uncontrolled hypertension as documented by 2 baseline blood pressure readings taken at least 1 hour apart. At least one of the baseline systolic blood pressure readings must be ≤150 mm Hg, and one of the baseline diastolic blood pressure readings must be ≤90 mm Hg. Patients whose hypertension is controlled by antihypertensive therapies are eligible.
14. Women of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to treatment.
15. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including tumour biopsies.
16. Written informed consent

5.4. EXCLUSION CRITERIA

1. The presence of intracranial disease, unless there has been radiological evidence of stable intracranial disease >6 months. In the case of a solitary brain metastasis which has been resected, there must be evidence of a disease-free interval of at least 3 months post-surgery. All patients previously treated for brain metastases must be stable off corticosteroid therapy for at least 28 days.
2. The presence of active second malignancy. Patients will be eligible if they have adequately treated basal cell carcinoma, squamous cell skin cancer, in situ cervical cancer, stable prostate cancer or if treated with curative intent for any other cancer with no evidence of disease for 2 years.
3. Women who are pregnant or are breastfeeding. Female patients must be surgically sterile, be postmenopausal, or must agree to use effective contraception during the period of therapy. All female patients with reproductive potential must have a negative pregnancy test (serum or urine) prior to enrolment.
4. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy.

5. Current signs or symptoms of severe progressive or uncontrolled hepatic, endocrine, pulmonary disease other than directly related to RCC.
6. Gastrointestinal abnormalities including:
    a. inability to take oral medication;
    b. requirement for intravenous alimentation;
    c. prior surgical procedures affecting absorption including total gastric resection;
    d. treatment for active peptic ulcer disease in the past 6 months;
    e. active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
    f. malabsorption syndromes.
7. Current use or anticipated need for treatment with drugs that are known potent CYP3A4 inhibitors (see section 8.12, concomitant therapy).
8. Current use or anticipated need for treatment with drugs that are known CYP3A4 or CYP1A2 inducers (see section 8.11, concomitant therapy).
9. Requirement of anticoagulant therapy with oral vitamin K antagonists. Low-dose anticoagulants for maintenance of patency of central venous access device or prevention of deep venous thrombosis is allowed. Therapeutic use of low molecular weight heparin is allowed.
10. Active seizure disorder, spinal cord compression, or carcinomatous meningitis.
11. Any of the following within 12 months prior to study entry: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack.
12. Deep vein thrombosis or pulmonary embolism within 6 months prior to study entry.
13. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.
14. Known galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption

5.5. LIFESTYLE GUIDELINES

During the study female patients of childbearing potential must take precautions to prevent pregnancy since the effects of axitinib on the foetus are unknown. Male patients with partners of childbearing potential must take precautions to prevent pregnancy of the partner since the effects of the drug on sperm are unknown. These restrictions should remain in force for 6 months from the last dose of axitinib. Drug interaction studies with oral contraceptives have not been performed, so barrier methods of contraception or abstinence should be considered. Adequate contraception should be discussed with the physician before the treatment starts. The definition of adequate contraception is a double barrier contraception (i.e., condom plus spermicide in combination with a female condom, diaphragm, cervical cap or intrauterine device).

5.6. SCREENING LOG

All participating sites will be required to keep a log of all patients with metastatic renal cell carcinoma discussed at MDT who are not immediately clinically indicated for cytoreductive nephrectomy. The information collected on the log will include:

- Date patient identified

- Screening outcome (patient approached/ineligible/accepted participation/declined participation)
- Reasons for not approaching / declining participation (if available)
- Trial ID (if applicable)

This information will be used by the TMG to monitor recruitment activity. No patient identifiable data will be sent to ICR-CTSU at this stage.

6. CONSENT & REGISTRATION

6.1. PROCEDURE FOR OBTAINING INFORMED CONSENT

The Principal Investigator (or designated individual) should discuss the trial with potentially eligible patients, describing the purpose, alternatives, drug administration plan, research objectives and follow-up of the study. Patients will be provided with a Research Ethics Committee approved patient information sheet and consent form for review and given sufficient time and a minimum of 24 hours to consider participation in the study. Once a decision has been made to enter into the trial, a signature should be obtained from the patient to confirm consent. Consent should be obtained before any trial specific assessments prescribed by the protocol are performed.

6.2. STUDY REGISTRATION

Registration should take place as close to the planned start date of axitinib as possible.

Participants will be registered centrally with the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU). An eligibility and registration checklist must be completed prior to registration.

The following information will be required at registration:

- Name of hospital, consultant and person registering patient
- Confirmation that patient has given written informed consent for trial participation and the provision of biological samples
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number (or equivalent)
- Date of diagnosis of metastatic RCC
- Proposed start date of axitinib

To register a patient telephone:

ICR Clinical Trials and Statistics Unit (ICR-CTSU)

The Institute of Cancer Research

020 8643 7150

09.00-17.00 (UK time) Monday to Friday

The caller will be given the patient's unique registration number (Trial ID). The Trial ID together with the patient's initials and date of birth should be used on all Case Report Forms (CRFs).

All registered A-PREDICT participants will receive axitinib therapy (see Section 8 - TRIAL treatment).

Written confirmation will be sent by fax to the data management contact and pharmacist at the registering centre to confirm trial entry.

7. TRIAL ASSESSMENTS & DISPENSING SCHEDULE

7.1. PRE-REGISTRATION ASSESSMENTS

The following screening procedures must be performed

7.1.1.WITHIN 21 DAYS PRIOR TO TRIAL REGISTRATION:

- Medical history
- Physical examination including ECOG performance status, body weight, height, temperature, blood pressure measurement (repeated twice as per inclusion criteria), heart rate, respiratory rate
- Haematology, coagulation, glucose, renal and liver function, serum calcium and LDH
- Urinalysis for protein
- Serum Thyroid Function Tests (Free T4 and TSH)
- Pregnancy test (serum or urine), if female and of child-bearing potential
- Baseline symptom assessment (NCI CTCAE v.4)
- CT thorax, abdomen and pelvis and tumour assessment using RECIST 1.1 criteria. CT must be conducted prior to the research biopsy.
- Mandatory percutaneous biopsy of non-necrotic region of primary renal tumour under ultrasound or CT guidance (see Appendix B Translational research studies)
- If possible, percutaneous biopsy of one metastatic site under ultrasound or CT guidance (see Appendix B Translational research studies).
- Histological confirmation of metastatic renal cell carcinoma from either site (if not previously confirmed)*.
- Assessment of concomitant medications

*NB If a patient consents to donate research biopsies but is subsequently found to be ineligible, these research biopsies should be notified to ICR-CTSU as described in Section 19.4.1 of the protocol: Tracking of baseline samples for ineligible patients

7.2. BASELINE ASSESSMENTS – PRETREATMENT DAY 1 WEEK 1

The following must be performed on **day 1 week 1** prior to starting the study drug unless conducted within previous 7 days as part of pre-registration assessments:

- Physical examination including ECOG performance status, body weight, temperature, blood pressure, heart rate, respiratory rate
- Haematology, coagulation, glucose, renal and liver function, serum calcium and LDH
- Urinalysis for protein

- Symptom assessment (NCI CTCAE v.4)
- Blood samples and urine sample for biomarker analysis (see Appendix B)
- Assessment of concomitant medications
- Pregnancy test if not conducted within 3 days of starting treatment

Dispense axitinib to patient (see section 8)

7.3. DAY 1 WEEK 3

The following investigations should be conducted on day 1 of week 3 (+/- 72hrs):

- Physical examination including ECOG performance status, body weight, temperature, blood pressure, heart rate, respiratory rate
- Symptom assessment (NCI CTCAE v.4)
- Serum Thyroid Function Tests (Free T4 and TSH)
- Assessment of concomitant medications

NB. If the participant has any axitinib treatment interruptions ≥ 1 week, please contact the trials office for advice on scheduling of subsequent follow up and research biopsy.

7.4. DAY 1 WEEK 5:

The following investigations should be conducted on day 1 of week 5 (+/- 72 hrs):

- Physical examination including ECOG performance status, body weight, temperature, blood pressure, heart rate, respiratory rate
- Haematology, coagulation, glucose, renal and liver function, serum calcium and LDH
- Urinalysis for protein
- Symptom assessment (NCI CTCAE v.4)
- Assessment of compliance with study medication
- Serum Thyroid Function Tests (Free T4 and TSH)
- Assessment of concomitant medications

NB. If the participant has any axitinib treatment interruptions ≥ 1 week, please contact the trials office for advice on scheduling of subsequent follow up and research biopsy.

Dispense axitinib to patient (see section 8)

7.5. DAY 1 WEEK 8

Patient should be instructed to stop axitinib 5-7 days prior to biopsy (after 7 weeks of treatment)

NB. If the participant has any axitinib treatment interruptions ≥ 1 week, please contact the trials office for advice on scheduling of subsequent follow up and research biopsy.

7.6. DAY 1 WEEK 9

The following investigations/assessments should be conducted on day 1 week 9 (+/- 72 hrs):

- Physical examination including ECOG performance status, body weight, temperature, blood pressure, heart rate, respiratory rate
- Haematology, coagulation, glucose, renal and liver function, serum calcium and LDH
- Urinalysis for protein
- Symptom assessment (NCI CTCAE v.4)
- Blood samples and urine sample for biomarker analysis (see Appendix B)
- CT thorax, abdomen and pelvis and assessment of response according to RECIST 1.1 criteria.
- Percutaneous biopsy of non-necrotic region of primary renal tumour (from same site as first biopsy if possible) via appropriate (US or CT) guidance (see Appendix B)
- Assessment of compliance with study medication (see section 8)
- Assessment of concomitant medications

Dispense axitinib, with instructions to patient to start 2-3 days after biopsy (see section 8)

NB: CT thorax, abdomen and pelvis should be carried out prior to biopsy

7.7. DAY 1 WEEK 13 (AND EVERY 4 WEEKS TO SIX YEARS/DISEASE PROGRESSION):

The following investigations should be conducted on of day 1 (+/- 72 hrs) of each 4-weekly visit.

- Physical examination including ECOG performance status, body weight, temperature, blood pressure, heart rate, respiratory rate
- Haematology, coagulation, glucose, renal and liver function, serum calcium and LDH
- Urinalysis
- Serum Thyroid Function Tests (Free T4 and TSH) should be conducted every 8 weeks from day 1 week 13
- Symptom assessment (NCI CTCAE v.4)
- Assessment of compliance with study medication (see section 8)
- Assessment of concomitant medications

Dispense axitinib to patient (see section 8)

After six years on treatment, the above investigations and assessments should be conducted every 12 weeks.

In addition, on day 1 week 17, day 1 week 25, and 12 weekly thereafter:

- CT thorax, abdomen and pelvis and assessment of response according to RECIST 1.1 criteria.

7.8. PROCEDURE IF PATIENT IS WITHDRAWN FROM AXITINIB TREATMENT

- CT thorax, abdomen and pelvis and assessment of response according to RECIST 1.1 criteria prior to commencement of any subsequent treatment

7.9. PROCEDURE AT DISEASE PROGRESSION:

Axitinib therapy should be continued until there is clinically significant disease progression, after which treatment should be discontinued and the following investigations should be conducted.

- Physical examination including ECOG performance status, body weight, temperature, blood pressure, heart rate, respiratory rate
- Haematology, coagulation, glucose, renal and liver function, serum calcium and LDH
- Toxicity assessment (NCI CTCAE v.4)
- CT thorax, abdomen and pelvis and assessment of response according to RECIST 1.1 criteria prior to commencement of any subsequent treatment
- Blood samples and urine sample for biomarker analysis (see Appendix B)
- Biopsy of site of progression, or if not possible, percutaneous primary tumour biopsy via appropriate (US or CT) guidance (see Appendix B), one week after stopping axitinib treatment. Biopsy should be taken prior to commencement of any subsequent treatment.
- Assessment of concomitant medications

7.10. NEPHRECTOMY GUIDELINES

Nephrectomy should be offered to any participant who becomes suitable in the opinion of the treating clinician during the course of the trial. Where possible, tissue samples should be provided from resected specimens (see Appendix B).

Axitinib must be stopped 5-7 days prior to nephrectomy. Patients may resume axitinib 2-3 weeks after nephrectomy. The decision to resume axitinib after any major surgical procedure, including nephrectomy, should be based on clinical judgement of adequate wound healing.

CT thorax, abdomen and pelvis and assessment with RECIST v1.1 criteria should be conducted within 21 days following surgery, and this scan should be used to provide a new baseline for subsequent response assessment.

7.11. FOLLOW UP

Patients should be followed up for survival and performance status every 12 weeks after treatment discontinuation.

7.12. WITHDRAWAL FROM TRIAL FOLLOW-UP

If a patient withdraws consent for further follow-up clarification should be sought to as to whether they no longer wish to attend trial specific follow up visits or wish to stop contributing further data to the study. In the unlikely event that the patient wishes to have their data removed from the trial completely (the implications of this should be discussed with the patient to ensure that this is their intent) this should be indicated on the relevant case report form and notified to the trial manager at ICR-CTSU.

7.13. SCHEDULE OF ASSESSMENTS

Visit/Assessment	Up to 21 days Pre-registration	Pre-treatment day 1 week 1*	Day 1 week 3	Day 1 week 5	Day 1 Week 8	Day 1 week 9	Day 1 week 13	Day 1 week 17	Day 1 week 21	Day 1 week 25#	Disease progression
Confirmation of histological diagnosis of metastatic renal cell carcinoma	X										
Medical history	X										
Physical examination including ECOG performance status, body weight, height, temperature, blood pressure[7], heart rate, respiratory rate	X	X	X	X		X	X	X	X	X	X
Haematology, coagulation, glucose, renal and liver function, serum calcium and LDH	X	X		X		X	X	X	X	X	X
Urinalysis for protein	X	X		X		X	X	X	X	X	
Symptom assessment (NCI CTCAE v.4)	X	X	X	X		X	X	X	X	X	X
Serum Thyroid Function Tests (Free T4 and TSH)	X		X	X			X[4]		X		
Pregnancy test (serum or urine) if applicable	X										
CT thorax, abdomen and pelvis and tumour assessment using RECIST 1.1 criteria	X[1]					X		X		X[5]	X
Percutaneous image guided biopsy of non-necrotic region of primary renal tumour and possibly one metastatic site (see Appendix B)	X[2]					X					X[6]
Blood samples and urine sample for biomarker analysis (Appendix B)		X				X					X
Assessment of compliance with study medication				X		X	X	X	X	X	
Dispense axitinib		X		X		X[3]	X	X	X	X	
Stop axitinib 5-7 days prior to biopsy					X						
Assessment of concomitant medications	X	X	X	X		X	X	X	X	X	X

- * Day 1 week 1 assessments may be omitted if conducted within previous 7 days as part of pre-registration assessments (apart from pregnancy test)
- # Subsequent visits to take place 4 weekly thereafter to six years, after which they should take place 12 weekly.

1. CT thorax, abdomen and pelvis should be conducted prior to biopsy
2. One week prior to starting axitinib if possible.
3. Patient to restart axitinib 2-3 days after biopsy
4. Subsequent thyroid function tests should be conducted every 8 weeks to six years, after which they should be conducted 12 weekly
5. Subsequent tumour imaging to be performed 12 weekly thereafter and at treatment discontinuation/progression
6. Biopsy of site of progression, or if not possible, percutaneous image guided primary tumour biopsy. Biopsy should be taken prior to commencement of any subsequent treatment.
7. Blood pressure readings are required at each clinic visit and should be taken in the seated position after the patient has been sitting quietly for 5 minutes. Two readings should be taken one hour apart at pre-registration visit. A consecutive reading should be taken at subsequent visits only if the first is elevated.

8. TRIAL TREATMENT

8.1. THERAPEUTIC REGIMEN AND DOSE MODIFICATIONS

- Axitinib treatment should commence on Day 1 of the study.
- Patients should be prescribed a starting dose of 5mg BID.
- Patients should be advised to stop axitinib treatment 5-7 days prior to day 1 week 9 tissue collection for the translational study and to restart 2-3 days post biopsy.
- Doses should be taken approximately 12 hours apart.
- Patients should be instructed to take their doses at approximately the same times each day.
- If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. If the patient reports having missed a dose or vomiting, this should be recorded in the source documents and CRFs.
- Dose adjustments, including dose increase or dose reduction, are permitted and should be based on clinical judgement and the guidelines provided in the following sections.
- Queries relating to potential dose adjustments should be discussed with ICR-CTSU. Consideration of dose adjustment guidelines and clinical rationale for dosing decision should be clearly documented in the patient's medical notes.

8.2. AXITINIB DOSE LEVELS

Dose Level	Dose	Dispensed As
+2	10 mg BID	2 X 5 mg tablets BID
+1	7 mg BID	1 X 5 mg tablet BID + 2 X 1mg tablets BID
0 (Starting Dose)	**5 mg BID**	**1 X 5 mg tablet BID**
-1	3 mg BID	3 X 1mg tablets BID
-2	2 mg BID	2 X 1mg tablets BID

8.3. DOSE ESCALATION SCHEDULE

Patients who tolerate axitinib with no adverse events related to study drug above CTCAE grade 2 for a consecutive 2-week period may have their dose increased by one dose level to a maximum of 10 mg BID (unless the patient's blood pressure [BP] is >150/90 mm Hg or the patient is receiving antihypertensive medication). If the patient is receiving antihypertensive medication and a dose escalation is clinically indicated the ICR-CTSU should be contacted to obtain TMG approval of the proposed dose escalation. No patient receiving antihypertensive medication should have an axitinib dose escalation without prior written confirmation from ICR-CTSU of TMG approval.

8.4. DOSE INTERRUPTION AND REDUCTION

Patients experiencing non-haematological drug reactions greater than CTCAE Grade 2 or haematological reactions greater than CTCAE Grade 3 should undergo dose modification. The current version of the SmPC should be used to assess whether any adverse event is attributable to the drug.

Axitinib should be stopped in the event of significant toxicity and restarted if appropriate when toxicities have resolved. Recovery to acceptable levels of toxicity must occur within 4 weeks to allow recommencement of treatment.

Patients permanently removed from treatment for intolerable toxicity should receive a post treatment CT scan assessed according to RECIST 1.1 criteria, and should continue to be followed with regular tumour assessments until disease progression or start of new treatment, and for survival thereafter.

The criterion for dose modification for axitinib related adverse events is summarised in the table below:

8.4.1. CRITERIA FOR DOSE MODIFICATION FOR AXITINIB - RELATED ADVERSE EVENTS (OTHER THAN HYPERTENSION OR PROTEINURIA)

Related Adverse Events	INTERVENTION
Any Grade: Bleeding where medical intervention is required	Temporarily interrupt the axitinib dose.
Any Grade: Posterior reversible encephalopathy syndrome (PRES)	Patients with signs or symptoms should temporarily interrupt or permanently discontinue axitinib treatment. In case of severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome, a diagnostic brain magnetic resonance image (MRI) should be considered.
Moderate hepatic impairment (Child-Pugh class B)	A dose decrease is recommended
Grade 1 or 2	Continue at same dose level
Grade 3 non-haematologic treatment-related toxicity	Decrease dose to one lower dose level unless controlled with symptomatic medications.
Grade 3 asymptomatic biochemistry laboratory abnormalities	Continue at the same dose level at the discretion of the investigator
Grade 4 non-haematologic treatment-related toxicity or Grade 4 haematologic toxicity (other than those below)	Interrupt dosing; re-start at one lower dose level as soon as improvement to CTCAE Grade ≤2. If patient requires dose reduction below 2 mg BID, contact ICR-CTSU for discussion prior to implementation.
Grade 4 lymphopaenia or Grade 4 asymptomatic biochemistry laboratory abnormality	Continue at the same dose level at the discretion of the investigator

Any Grade: Cardiac Failure Events	Management may include temporary interruption and possible dose reduction OR permanent discontinuation of axitinib.

8.5. AXITINIB DOSE REDUCTION GUIDANCE FOR HYPERTENSION

Guidance on dose interruption and reduction for hypertension is summarized in the table below. Queries relating to hypertension management should be discussed with ICR-CTSU

HYPERTENSION MANAGEMENT PLAN FOR AXITINIB			
Degree of Blood Pressure Elevation			**Management**
Systolic Pressure		Diastolic Pressure	
2 consecutive BP readings show systolic pressure >150 mmHg	OR	2 consecutive BP readings show diastolic pressure >90 mmHg	If not on maximal antihypertensive treatment, institute new or additional antihypertensive medication and maintain dose of axitinib. If on maximal antihypertensive treatment, reduce axitinib to one lower dose level.
2 consecutive BP readings show systolic pressure >160 mmHg	OR	2 consecutive BP show diastolic pressure >100mmHg	Interrupt dosing*; adjust antihypertensive medication; as soon as BP is less than 150/90 mmHg, restart axitinib at one lower dose level.
Persistent hypertension (2 consecutive BP readings show systolic pressure >150 mmHg) following previous dose reduction for hypertension	OR	Persistent hypertension (2 consecutive BP readings show diastolic pressure >90 mmHg) following previous dose reduction for hypertension	Repeat axitinib dose reduction by one lower dose level. If a patient requires dose reduction below 2 mg BID, contact ICR-CTSU for discussion

* If dose is interrupted, patients receiving antihypertensive medications should be monitored closely for hypotension.

8.6. AXITINIB DOSE REDUCTION FOR PROTEINURIA

- If dipstick shows > 1+ proteinuria, perform 24 hour urine collection or urinary protein:creatinine ratio (PCR). Dosing may continue while waiting for test results.
- If < 2g proteinuria/24 hour or urinary PCR < 200mg/mmol is reported, continue dosing at the same dose level.
- If ≥ 2g proteinuria/24 hours or urinary PCR ≥ 200mg/mmol is reported, withhold dose and repeat 24 hour urine collection for proteinuria and creatinine clearance (interval at investigator discretion) until proteinuria is < 2 g/24 hours or urinary PCR < 200mg/mmol. Restart axitinib at the same dose or one lower dose level at discretion of the investigator.
- If patient develops nephrotic syndrome axitinib should be discontinued.

8.7. DOSE RE-ESCALATION

Re-escalation back to the previous dose level is permitted in the absence of grade ≥3 haematologic or grade ≥2 non-haematologic treatment-related toxicity in the previous 4 weeks of treatment.

8.8. AXITINIB DOSE INTERRUPTION FOR SURGERY OR SURGICAL PROCEDURES

If major surgery or an interventional procedure (e.g. endoscopy) which is not part of the A-PREDICT translational study is required, treatment with axitinib must be interrupted at least 24 hours before the procedure and the patient blood pressure should be monitored closely for hypotension. Patients may resume axitinib seven days after minor surgery and 2-3 weeks after major surgery, assuming the wound has completely healed. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

8.9. DURATION OF THERAPY

In the absence of unacceptable toxicity treatment should continue until the patient is no longer deriving clinical benefit.

Patients may also discontinue protocol treatment in the following instances:

- Intercurrent illness which would in the judgment of the investigator affect patient safety, the ability to deliver treatment or the primary study endpoints
- Request by patient

Patients for whom treatment is discontinued should be followed for disease progression and for survival thereafter according to the Schedule of Assessments (see section 7).

8.10. SUPPORTIVE CARE GUIDELINES

Palliative and supportive care for disease-related symptoms, including pain medications and palliative radiotherapy, is permitted. Patients may receive loperamide or other medications for treatment or prophylaxis of potential diarrhoea. Anti-inflammatory or narcotic analgesics may be offered as needed. Patients with fever or infection may undergo diagnostic tests and be treated with antibiotics as appropriate and may receive therapeutic colony-stimulating factors as appropriate. Erythropoietic agents such as epoetin or darbepoetin may be used at the discretion of the treating physician. Packed red blood cell and platelet transfusions should be administered as clinically indicated. Low-dose oral steroids (defined as <5 mg per day prednisone or equivalent), short course of more potent oral steroids (defined as < 5 consecutive days) or topical or inhaled steroids at any dose may be taken during the study.

Patients who need to be on anticoagulant therapy during treatment with axitinib should be treated with low molecular weight heparin as the preferred therapy. The administration of coumadin or other coumarin derivatives may be allowed; however, due to possibility of inhibition of CYP1A2-mediated metabolism of coumadin by axitinib, appropriate monitoring of PT/INR should be performed for any potential increased coumadin concentration.

Patients receiving axitinib should be monitored for signs and symptoms of hypothyroidism, such as fatigue, deepening of voice, cold intolerance, constipation, anorexia, periorbital edema, myxedema, or changes in skin or hair. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state.

8.11. CONCOMITANT THERAPY

Axitinib is metabolised primarily by liver enzymes, in particular CYP3A4. All medication considered necessary for the patients' welfare and which is not expected to interfere with the evaluation of the

study drugs may be given at the discretion of the investigator. Concomitant medications must be recorded in the patient's source documentation, as well as the appropriate pages of the CRF.

Contraindicated concurrent medications include:

- Agents known to induce CYP3A4/5 or CYP1A2 including:
    - carbamazepine,
    - dexamethasone,
    - felbamate,
    - omeprazole,
    - phenobarbital,
    - amobarbital,
    - phenytoin,
    - primidone,
    - rifabutin,
    - rifampicin,
    - nevirapine,
    - St John's wort
    - rifapentin
- Agents known to inhibit CYP3A4/5 including:
    - grapefruit juice,
    - ketoconazole,
    - miconazole,
    - itraconazole,
    - erythromycin,
    - clarithromycin,
    - telithromycin,
    - verapamil,
    - indinavir,
    - saquinavir,
    - ritonavir,
    - nelfinavir,
    - lopinavir,
    - atazanavir,
    - amprenavir,
    - fosamprenavir
    - delavirdine
    - nefazodone
- Other approved or investigational systemic anticancer treatments, including chemotherapy, hormone therapy and immunotherapy
- Other investigational drugs

The use of potent antacids such as proton pump inhibitors (except those listed above) and histamine H_2 antagonists is permissible, if medically necessary. However, patients requiring chronic antacid therapy should avoid their use for 2 hours before and for 2 hours after taking axitinib tablets.

The contraindicated medications detailed above may only be used in exceptional circumstances and following written confirmation from the ICR-CTSU of the Chief Investigator's approval.

The current version of the SmPC should be used to assess whether any other concomitant medications are permissible.

8.12. SUBSEQUENT THERAPY

Participants for whom treatment is discontinued should be treated according to clinical circumstances and should be managed at the local clinician's discretion.

8.13. DRUG COMPLIANCE AND ACCOUNTABILITY

The study drug must not be used outside the context of the A-PREDICT protocol. Patients must be asked to bring all their trial medication every time they attend the clinic for the purposes of treatment compliance assessment and drug accountability. Every effort should be made to encourage patients to return the unused medication and empty packs/bottles. The unused tablets should be collected by the investigator/study nurse and counted to ascertain patient compliance, medication will then be returned

to pharmacy for drug accountability prior to destruction according to local practices. Drug accountability and destruction records should be maintained by the local pharmacy.

8.14. AXITINIB MANUFACTURER

Axitinib (also known as AG-013736) is manufactured and provided free of charge by Pfizer to participating centres.

8.15. PACKAGING AND LABELLING

Axitinib is presented as 1mg and 5mg immediate release film-coated tablets and supplied in HDPE (Heavy Duty Polyethylene) bottles, with induction seals. Tablet bottles of each dose contain 60 tablets.

Pfizer will coordinate study drug packaging, labelling and distribution for this trial. The schedule of responsibilities for this arrangement is detailed in a contract between Pfizer and the Co-sponsors.

Labelling will be the responsibility of Pfizer and will be compliant with Annex 13 of the Good Manufacturing Guidelines (GMP) and all applicable local regulatory requirements.

8.16. DRUG STORAGE

Axitinib should be stored in the original package in order to protect from moisture and should be stored at controlled room temperature (between 15°C and 30°C) and protected from light. The local pharmacy is responsible for ensuring that the study medication is stored in an appropriate secured area.

8.17. DISTRIBUTION OF DRUGS TO SITE

ICR-CTSU will arrange for a supply of the study drugs to be sent from Pfizer to the relevant pharmacy department following centre initiation. Local R & D approval and a study agreement must be in place before any drug can be shipped to sites.

8.18. COMMERCIAL SUPPLY

After November 2018 A-PREDICT participants still receiving axitinib will be transferred to free of charge commercial supply. Commercial supply will be provided by Pfizer until A-PREDICT participants' treatment discontinuation.

Commercial supply axitinib will be labelled by the local site's pharmacy prior to dispensing in accordance with the MHRA approved A-PREDICT commercial supply label contents. Axitinib should be stored as per section 8.16 of the protocol.

Pfizer are responsible for distribution of commercial supply axitinib to participating sites.

8.19. PHARMACY RESPONSIBILITIES AND DRUG ACCOUNTABILITY

8.19.1. LABELLING

Pharmacies may add their own hospital dispensing label to the study drug which must not obscure the existing label on the drug packaging.

8.19.2. ACCOUNTABILITY

The local pharmacy department must designate a responsible person for ensuring that:

- the study drug is handled and stored safely and properly;
- the study drug label is completed for each patient in accordance with Annex 13 of the EU Good Manufacturing Practice (GMP) Guidelines;
- the study drug is dispensed only to trial patients and in accordance with the protocol;
- full accountability of the study drug is maintained
- there is a sufficient supply of study drug for patients' continued treatment, and in a timely manner contact ICR-CTSU for re-supply of stock;
- study drug expiry dates are monitored and are used in order of expiry date order i.e. earliest expiry first;
- unused study drug is destroyed locally in accordance with hospital protocol.

Records must be kept of all deliveries, dispensing and destruction in accordance with the A-PREDICT Pharmacy Guidance Notes. These records may be requested by ICR-CTSU during the trial to monitor supply and usage of stock. Account must be given of any discrepancies and certificates of delivery and return must be signed.

8.20. PATIENT CARDS

Small wallet sized cards will be produced by ICR-CTSU on request by the participating centre. Each card will state:

- the name and emergency contact details of the participating centre
- that the patient is participating in the A-PREDICT trial
- that the patient is taking axitinib

9. PHARMACOVIGILANCE

9.1. DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a study drug, whether or not considered related to the study drug. Signs and symptoms of metastatic disease, as determined by the local clinical investigator, are not adverse events.*

Adverse Reaction (AR): all untoward and unintended responses to the study drug related to any dose administered. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE): Any untoward medical occurrence or effect which occurs within 28 days of the patient receiving study drug that at any dose:

- results in death: the patient's death is suspected as being a direct outcome of the AE.

- is life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It also refers to an event that would result in death with the continued use of the product; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires hospitalisation, or prolongation of existing inpatient hospitalisation: admission to hospital overnight or prolongation of a stay in hospital was necessary as a result of the AE. Outpatient treatment in an emergency room is not itself an SAE, although the reasons for it may be. Hospital admissions/surgical procedures planned for a pre-existing condition before a patient is registered to the study are not considered SAEs, unless the illness/disease deteriorates in an unexpected way during the study.
- results in persistent or significant disability or incapacity: the AE results in a significant or persistent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- is a congenital anomaly or birth defect
- death due to progressive disease

Progression of the malignancy should NOT be reported as an SAE. Hospitalisation due to signs and symptoms of malignancy progression does NOT require reporting as an SAE

Medical judgement should be exercised in deciding whether other AEs are serious. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Serious Adverse Reaction (SAR): Any serious adverse event judged by either the Principal Investigator or the Chief Investigator as having suspected causal relationship to the study drug.

Suspected Unexpected Serious Adverse Reaction (SUSAR): Any serious adverse event judged by either the Principal Investigator or the Chief Investigator as having suspected causal relationship to the study drug that is not listed on the SmPC and, in the opinion of the Chief Investigator, is unexpected.

9.2. CAUSALITY

The Principal Investigator and the Chief Investigator must assess whether Serious Adverse Events have a suspected causal relationship to the study drug. A suspected causal relationship is defined as possibly, probably or definitely related (see definitions of causality table).

9.3. DEFINITIONS OF CAUSALITY

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the

	patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

If there is any doubt about the causality of an event, the investigator should contact ICR-CTSU who will discuss with the Chief Investigator. The drug manufacturer and/or other clinicians may also be asked for advice.

9.4. DEFINITIONS OF EXPECTEDNESS

Expected adverse events are those which are expected to occur, according to previous clinical experience, and are listed in the SmPC. The expectedness of an SAE will be assessed by the Chief Investigator (or the CI's delegate).

9.5. REPORTING SERIOUS ADVERSE EVENTS TO ICR-CTSU

Any SAE that occurs from the time of registration and up to 28 days following the last dose of axitinib must be reported.

All SAEs should be reported to ICR-CTSU, within 24 hours of the Principal Investigator (or designated representative) becoming aware of the event, by completing the trial specific SAE forms and faxing to:

The ICR-CTSU safety desk

Fax no: 0208 722 4368

For the attention of the A-PREDICT Trial team

All SAE forms must be completed, signed, and dated by the Principal Investigator or designated representative.

9.6. REVIEW OF SERIOUS ADVERSE EVENTS

The Chief Investigator (or designated representative) will assess all reported SAEs for causality and expectedness.

NB. The Chief Investigator cannot down-grade the Principal Investigator's assessment of causality.

SAEs assessed as having a causal relationship to study drug and as being unexpected (SUSARs) will undergo expedited reporting to the relevant authorities by ICR-CTSU (see figure 3 for SAE reporting).

Centres should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of the SAE.

All reported SAEs and follow up information will be forwarded to Pfizer upon receipt at ICR-CTSU.

9.7. EXPEDITED REPORTING OF SUSARS

If an SAE is identified as being a SUSAR by the Chief Investigator, and is fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the Main REC, the sponsor institutions and Pfizer within 7 days of being notified of the event.

If an SAE is identified as a SUSAR by the Chief Investigator, and is not fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the Main REC, the sponsor institutions and Pfizer within 15 days of ICR-CTSU being notified of the event.

ICR-CTSU will report any additional relevant information to the MHRA, Main REC, the sponsor institutions and Pfizer as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR.

The Principal Investigators at all actively recruiting centres will be informed of any SUSARs occurring within the trial at regular intervals.

9.8. FOLLOW UP OF SERIOUS ADVERSE EVENTS

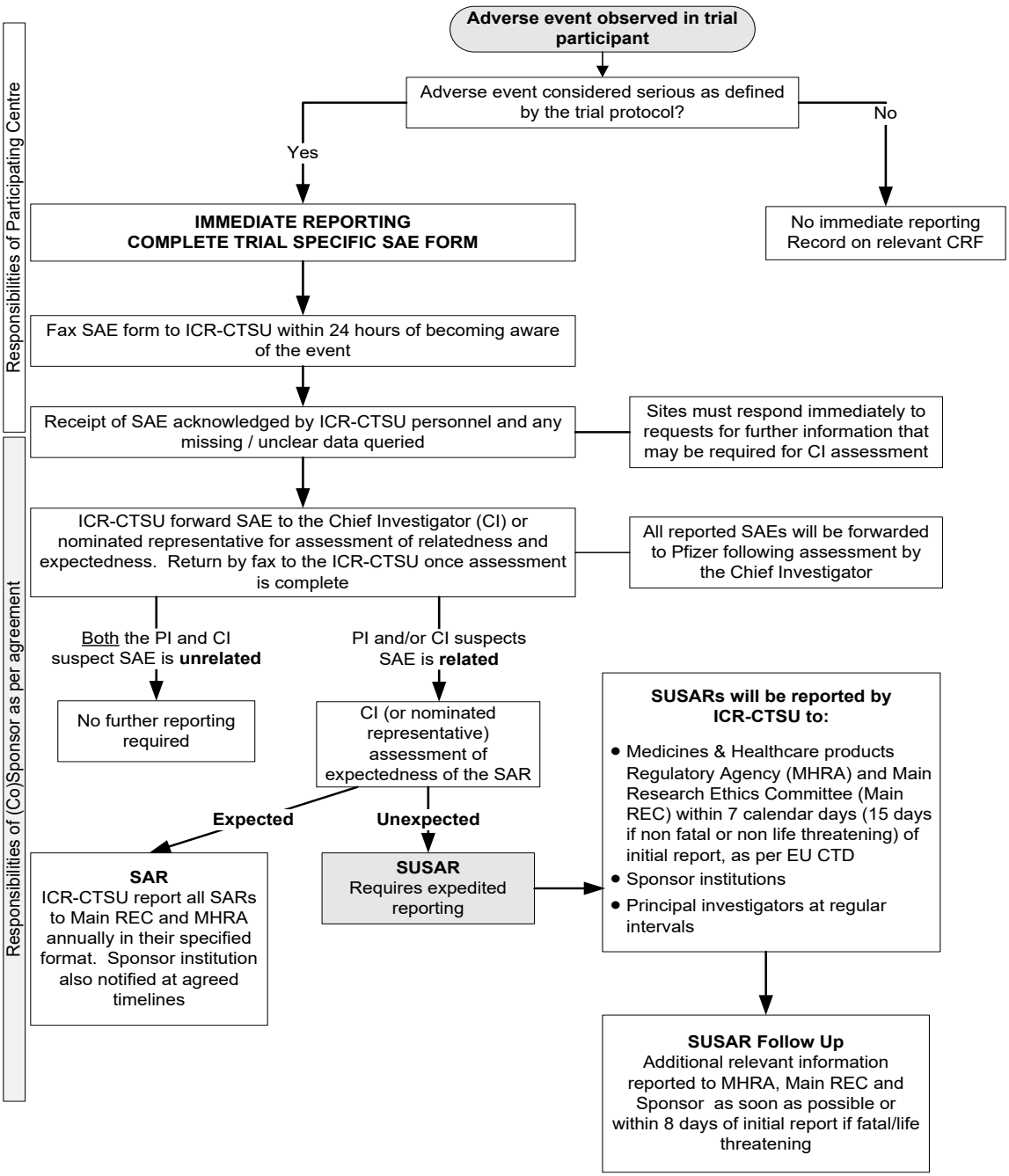
Centres should continue to follow up SAEs until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. SAE outcomes should be reported to ICR-CTSU using the relevant section of the SAE form as soon as the Principal Investigator becomes aware of the outcome.

NB. Any female patient who becomes pregnant or the partner of any male patient who fathers a child whilst on study medication, must be followed up and the outcome reported to ICR-CTSU who will then forward the details to Pfizer.

9.9. ANNUAL REPORTING OF SERIOUS ADVERSE REACTIONS

An annual report will be provided to the MHRA and the Main REC by ICR-CTSU and copied to the sponsors at the end of the reporting year. This will be defined as the anniversary of the date when the Clinical Trials Authorisation (CTA) was obtained. This will include all related events reported on SAE forms, and a report from the Independent Data Monitoring and Steering Committee (IDMSC).

9.9.1. FIGURE 3 - FLOW DIAGRAM FOR SAE REPORTING, AND ACTION FOLLOWING REPORT



NB. All SAEs should continue to be followed up as specified in the protocol.

10. STATISTICAL CONSIDERATIONS

10.1. STATISTICAL DESIGN AND SAMPLE SIZE JUSTIFICATION

This study is designed to assess the efficacy of axitinib in patients with mRCC not immediately clinically indicated for nephrectomy, a very poor risk group of patients. The median progression free survival for poor risk patients with mRCC treated with temsirolimus, the standard of care in this setting, is approximately 5.5 months[17]. Some benefit is expected for patients treated with axitinib, but the

expected degree of benefit is not known, nor is it known whether there will be a benefit via an increased response rate, or a prolongation of response, or both, detectable in PFS at 6 months.

Using a Simon Optimal Two-Stage design this study has 90% power at a one-sided significance level of 0.05 to discount an 'ineffective' rate of freedom from progression at 6 months (PFS6) of 25% (p0) in favour of a PFS6 of at least 40% (p1). This point estimate (40%) is lower than perhaps expected for temsirolimus (ignoring the inevitable variability around these estimates). However, a slightly lower threshold for axitinib may be acceptable given it is well tolerated and an oral compound, thus requiring fewer visits to hospital than for an IV drug such as temsirolimus.

37 patients will be treated in stage one and, if successful, a further 62 patients in stage two bringing the total number of patients required to 99. There will be no planned stopping in recruitment between stages 1 and 2; patients will be entered into stage 2 whilst stage 1 patients are progressing through the trial, their data being analysed and reviewed by the Independent Data Monitoring and Steering Committee (IDMSC).

The trial will stop and the treatment will be rejected if there are fewer than 11 patients alive and progression free at 6 months when the first 37 patients have been on trial for 6 months. If 11 or more of the first 37 patients are alive and progression free at 6 months a further 62 patients will be recruited into the second stage. If there are 32 or more patients of the overall 99 entered alive and progression free at 6 months axitinib will be considered to have shown worthwhile efficacy, but not if there are 31 or less. Planning for a phase III trial can commence at any stage if 32 patients have been observed to be alive and progression free at 6 months. No data will be released from stage 1 whilst recruitment to stage 2 is ongoing unless advised to do so by the IDMSC .

10.2. ENDPOINT DEFINITIONS

10.2.1. PRIMARY ENDPOINT

The proportion of study participants alive and progression free at 6 months (day 1 week 25 visit). Progression will be measured from the date of study entry (registration date) until the first date of either death or confirmed progressive disease according to RECIST. Patients alive and free from progression will be censored at the date of last follow-up. The proportion of patients progression free at 6 months will be reported with 95% confidence interval. In addition, progression free survival will be presented using the Kaplan Meier product limit method with median progression free survival reported.

A blinded central review of CT scans will be conducted for verification purposes.

10.2.2. SECONDARY ENDPOINTS

Best overall response is defined as the best tumour response that is achieved during or within 30 days after termination of axitinib that is confirmed according to RECIST.

Progression-free survival (PFS) will be measured from the date of registration until first date of either death or confirmed progressive disease according to RECIST 1.1. Time to last follow-up will be used if patient has not progressed or died and PFS time for the patient will be considered censored. A Kaplan Meier graph and median survival time will be presented.

Overall survival will be measured from the date of registration until the date of death due to any cause. Time to last follow-up will be used if patient has not died and survival time for the patient will be considered censored. A Kaplan Meier graph and median survival time will be presented.

Safety and toxicity will be assessed throughout the treatment period using the NCI CTC AE v 4.0 and summarised in tabular format. Reported toxicities will be coded using MedDRA (current version).

The proportion of patients who undergo nephrectomy following registration as a result of treatment with axitinib will be reported with 95% confidence intervals.

10.2.3. EXPLORATORY ENDPOINTS

Analysis of response by biomarker sub-group will be descriptive in nature. Fisher's Exact Tests are likely to be reported, however, they will only be used for hypothesis generation due to the limited power of the study. Correlation between biomarker sub-groups and reported toxicity will also be explored via interaction tests. A false discovery rate of <5% will be applied to all biomarkers.

CT scans collected for central verification of the primary endpoint will be used to determine the extent of venous tumour thrombus in the IVC for each participant and the effect of axitinib treatment on VTT. The primary objective of this exploratory analysis will be to establish the proportion of patients with a reduction in Neves' classification (level of the VTT within the IVC) [30]. Secondary objectives will be to assess the height of the VTT above the ostium of the renal vein/IVC in this patient population and change in texture of IVC VTT following treatment with axitinib.

10.3. INTERIM ANALYSIS AND DATA MONITORING

An Independent Data Monitoring Committee will meet approximately every 6 months to review accrual, safety and efficacy data. The subsequent replacement of patients who withdraw from treatment or who are unevaluable for reasons deemed not to be treatment related will be based on the advice of this committee. For completeness a sensitivity analysis of the progression free rate calculated by the Kaplan Meier product limit method will also be presented in which withdrawals are censored.

A formal interim analysis will be conducted once the first 37 patients have at least 6 months follow up data available. The principal analysis for publication will occur on the recommendation of the IDMSC and is expected once 99 patients have at least 6 months follow up data available (or have died).

11. TRIAL MANAGEMENT

11.1. TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, Co-investigators and identified collaborators, the Trial Statistician and the Trial Managers. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of centres and professional groups. Where possible, membership will include a lay/consumer representative. Notwithstanding the legal obligations of the Co-Sponsors and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU and based on MRC Good Clinical Practice (MRC GCP). Use of biological samples or study data for purposes additional to those described within the protocol must be approved by the A-PREDICT Trial Management Group.

11.2. INDEPENDENT DATA MONITORING AND STEERING COMMITTEE (IDMSC)

The roles of the IDMC and TSC will be combined, i.e. the committee will both monitor the data produced by the trial, put these data into overall context and supervise the progress of the trial towards its interim and overall objectives. This committee will be constituted according to MRC Good Clinical Practice (MRC GCP) and will oversee the safety of the trial.

The IDMSC will meet in confidence at regular intervals, and at least annually. A report of the findings and recommendations will be produced following each meeting. This report will be submitted to the TMG and if required, the main REC and the MHRA.

The IDMSC reserve the right to release any data on outcome or side-effects to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

12. RESEARCH GOVERNANCE

This Clinical Trial will be conducted in accordance with the ethical principles laid down by the Declaration of Helsinki, 1964 and as amended in 1996 and the principles of Good Clinical Practice.

12.1. SPONSOR RESPONSIBILITIES

The Co-sponsors are The Institute of Cancer Research (ICR) and The Royal Marsden NHS Foundation Trust (RMH). Sponsorship activities and delegated responsibilities are shared between ICR and RMH, in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. Responsibilities of the Co-sponsors are set out in an agreement between ICR and RMH.

12.2. PRINCIPAL INVESTIGATOR RESPONSIBILITIES

Responsibilities of each Principal Investigator and participating centre will be detailed in a contract with the Co-sponsors.

Principal Investigator responsibilities include putting and keeping in place arrangements to run the trial at their site according to the trial protocol and applicable guidance notes, The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. The above responsibilities include, but are not limited to, the following:

- Putting and keeping in place arrangements to adhere the principles of GCP
- Keeping a copy of all 'essential documents' (as defined under the principles of GCP) and ensuring appropriate archiving and destruction of documentation once the trial has ended as required by regulation 31 of the principal Regulations of the Medicines for Human Use (Clinical Trials) Regulations 2004 implementing the commission directive 2005/28EC
- Ensuring investigational medicinal products (IMPs) are made available to subjects free of charge
- Taking appropriate urgent safety measures and
- Ensuring recording and prompt reporting of SAEs/SARs to ICR-CTSU

ICR is responsible for co-ordinating any required legal agreements and investigator statements.

The delegation of sponsorship responsibilities does not impact on or alter standard NHS indemnity cover. The agreement of delegated responsibilities is viewed as a partnership and as such it is necessary to share pertinent information between ICR and RMH/Chief Investigator, including proposed inspections by the MHRA and/or other regulatory bodies.

12.3. PFIZER RESPONSIBILITIES

Pfizer are responsible on behalf of the co-sponsors for the manufacture, packing, labelling and distributing of study drug to site in accordance with Good Manufacturing Practice and all applicable local legislation. Responsibilities are defined in an agreement between Pfizer and the co-sponsors.

13. TRIAL ADMINISTRATION & LOGISTICS

13.1. SITE ACTIVATION

Before activating the trial, participating centres are required to sign an agreement accepting responsibility for all trial activity which takes place within their centre.

Sites may commence recruitment once centre agreements have been signed by both parties, trial documentation is in place and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

13.2. DATA ACQUISITION

Electronic (e) Case Report Forms (CRF) will be used for the collection of trial data. ICR-CTSU will provide guidance to sites to aid the completion of the eCRFs. The Trial Management Group reserves the right to amend or add to the eCRF template as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres in accordance with the guidelines provided by ICR-CTSU.

By participating in the A-PREDICT trial, the Principal Investigators at each centre are confirming agreement with his/her local NHS Trust to ensure that:

- Sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and eCRFs;
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
- All staff at their centre who are involved with the trial will meet the requirements of the EU Directive;
- Original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent;
- All essential documents must be retained for five years after the Trial ends to comply with current legislation.
- Staff will comply with the protocol and Trial Guidance Notes for the A-PREDICT trial.

13.3. CENTRAL DATA MONITORING

Once data has been entered by the site personnel on the eCRF, ICR-CTSU will review it for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be issued to the centre for resolution.

Any systematic inconsistencies identified may trigger monitoring visits to centres.

13.4. ON-SITE MONITORING

If a monitoring visit is required, ICR-CTSU will contact the centre to discuss dates of proposed visit. Once a date has been confirmed, the centre should ensure that the relevant patient notes are available for monitoring.

ICR-CTSU and/or Francis Crick Institute staff conducting on-site monitoring will review essential documentation, carry out source data verification and monitor pharmacy and translational study procedures to confirm compliance with the site agreement and trial protocol to ensure the protection of patients' rights as detailed in the Declaration of Helsinki 1964 as amended October 1996.

If any problems are detected during the course of the monitoring visit, ICR-CTSU will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

13.5. COMPLETION OF THE STUDY AND DEFINITION OF STUDY END DATE

The study end date is deemed to be the date of last data capture.

13.6. ARCHIVING

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. They should be retained for a sufficient period (and at least 5 years after the date of last data capture) for possible inspection by the regulatory authorities. Documents should be securely stored and access restricted to authorised personnel.

14. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

This trial has been formally assessed for clinical risk by ICR-CTSU.

The trial has received ethical and regulatory approval. Before entering patients, the Principal Investigator at each site is responsible for submitting Site Specific Information and gaining local Research and Development approval of this protocol.

Patients should be asked to sign the trial consent forms at trial entry after receiving both verbal and written information about the trial. All consent forms must be countersigned by the Principal Investigator or a designated individual. A Delegation of Responsibilities Log, listing the designated individuals and the circumstances under which they may countersign consent forms, must be maintained at the participating centre. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The A-PREDICT patient information sheets should be provided in addition to any standard patient information sheets that are provided by the centre and used in routine practice.

14.1. PATIENT CONFIDENTIALITY

Patients will be asked to consent to their full name being collected at registration in addition to their date of birth, hospital number, postcode and NHS number (CHI in Scotland) to allow linkage with routinely collected NHS data and ensure accuracy in handling biological samples. The personal data recorded on all documents will be regarded as confidential, and any information which would allow individual patients to be identified will not be released into the public domain.

Each investigator should keep a separate log of all patients' Trial IDs, names, addresses and hospital numbers. The investigator must maintain trial documents, which are to be held at the participating centres (e.g. patients' written consent forms), in strict confidence. The investigator must ensure the patients' confidentiality is maintained at all times.

ICR-CTSU will maintain the confidentiality of patients at all times and will not reproduce or disclose any information by which patients could be identified. Representatives of ICR-CTSU and the regulatory authorities will be required to have access to patients notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

14.2. DATA PROTECTION ACT (DPA)

ICR-CTSU will comply with all aspects of the DPA 1998. Any requests from patients for access to data about them held at ICR-CTSU will be referred to the Data Protection Officer at The Institute of Cancer Research.

14.3. LIABILITY

Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

15. FINANCIAL MATTERS

The trial is investigator designed and led and has been endorsed by Clinical Trials Awards & Advisory Committee (CTAAC) of Cancer Research UK, and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

The trial has received an Investigator Initiated Research grant (IIR) from Pfizer. If further funding is received from any other source this will be made apparent in the patient information sheet and to the approving Main REC, but will not require a protocol amendment.

NCRN (or regional equivalent) network resources should be made available for A-PREDICT, as the trial is part of the NIHR portfolio by virtue of its endorsement by CTAAC.

16. PUBLICATION POLICY

The main trial results will be published in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, consisting of members of the Trial Management Group, and participating clinicians. All participating clinicians will be acknowledged in the publication. All presentations and publications relating to the trial must be authorised by the Trial Management Group. Authorship of any secondary publications e.g. relating to the various biological studies will reflect the intellectual and time input into these studies, and will not be the same as on the primary publication. No investigator may present or attempt to publish data relating to the A-PREDICT trial without prior permission from the Trial Management Group.

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18. APPENDIX A: RECIST

Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 criteria should be used for the assessment of treatment outcomes.

18.1. EVALUATION OF MEASURABLE AND NON-MEASURABLE LESIONS

- **Measurable disease** – the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology / histology.
- **Measurable lesions** – lesions that can be accurately measured in at least one dimension with the longest diameter ≥ 20 mm by chest X-ray, or ≥ 10 mm by CT/MRI scan or clinical exam.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Malignant lymph nodes must be ≥15 mm in the short axis when assessed by CT scan to be considered measurable.
- **Non-measurable lesions** – all other lesions, including small lesions and malignant lymph nodes (longest diameter <10 mm, or pathological lymph nodes with ≥10 to <15 mm short axis) i.e., leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, blastic bone lesions and also abdominal masses that are not confirmed and followed by imaging techniques.
- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- The utilisation of endoscopy and laparoscopy for objective tumour evaluation is not advised. The utilisation of such techniques should be restricted to confirming complete pathological response when biopsies are obtained.

18.2. BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest

lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All screening evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.
- The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow up.
- A sum of the longest diameters (LD) for all target lesions will be calculated and reported as the baseline sum of LD. The baseline sum LD will be used as reference by which to characterise the objective tumour.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

18.3. RESPONSE CRITERIA

18.3.1. DOCUMENTATION OF NEW LESIONS

- The presence of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions).
- A lesion identified at a follow-up visit in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

18.3.2. LESIONS THAT BECOME ‘TOO SMALL TO MEASURE’

- If lesions or lymph nodes recorded as target lesions at baseline become too faint on CT scan to assign an exact measure, a default value of 5mm should be assigned. This default value is derived from the 5mm CT slice thickness
- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm.

18.4. EVALUATION OF TARGET LESIONS

Response criteria	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions (lymph nodes must be <10mm short axis)
Partial Response (PR)	At least 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum of LD.
Progressive Disease (PD)	At least 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started and at least 5mm absolute increase in this sum or the appearance of one or more new lesions.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

18.5. EVALUATION OF NON-TARGET LESIONS

Response criteria	Evaluation of non-target lesions
Complete Response (CR)	Disappearance of all non-target lesions
Incomplete response / Stable disease (SD)	Persistence of one or more non-target lesions
Progressive disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions *

* To achieve 'unequivocal progression' on the basis of the 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 quality for unequivocal progression status. Although a clear progression of a non-target lesion is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or Chief Investigator).

18.6. EVALUATION OF OVERALL RESPONSE

The table below provides a summary of the overall response calculation at each time point.

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
CR	Not-evaluated*	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

18.7. CONFIRMATION OF DISEASE PROGRESSION

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

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

18.8. DURATION OF OVERALL RESPONSE

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

18.9. DURATION OF STABLE DISEASE

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

18.10. EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the study treatment until disease progression. The patient's best overall response assignment will depend on the findings of both target and non-target disease and the appearance of new lesions.

Best overall response is defined as the best response across all time points. For example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR.

18.11. CENTRAL REVIEW

Blinded central review of objective responses will be conducted in order to protect against any reporting bias.

19. APPENDIX B TRANSLATIONAL RESEARCH STUDIES

19.1. INTRODUCTION

A key aim of this study is to evaluate changes in circulating and tumour biomarkers in relation to tumour response. These biomarkers are developing from ongoing whole genome functional RNAi studies in renal cancer model systems and from synthetic lethal mTOR inhibitor and hypoxia RNAi screens conducted within the Francis Crick Institute.

The expression of these putative biomarkers of renal cancer response will be evaluated in tissue donated before and during treatment to define therapeutic response to treatment. In addition, novel techniques (including large scale DNA sequencing and SNP genotyping analyses) will be applied to samples to identify whether germline DNA, genomic tumour DNA, circulating tumour DNA, and circulating microRNAs can guide the identification of patients with disease sensitive to axitinib and provide insight into resistance mechanisms associated with axitinib treatment.

Analysis of tissue for such studies will be performed at the Francis Crick Institute.

19.2. A-PREDICT LABORATORY MANUAL

Detailed instructions for sample collection, processing, labelling, storage and transportation are provided in the A-PREDICT laboratory manual which is available on request from ICR-CTSU and should be referred to in conjunction with this protocol.

19.3. TISSUE ACQUISITION AND PROCESSING AT SITE

19.3.1. BASELINE PRIMARY TUMOUR TISSUE SAMPLE

Image guided percutaneous biopsy of the primary tumour should be performed prior to starting treatment. Five tissue cores from one needle puncture should be obtained; one should be sent for paraffin embedding and analysis by the local pathologist to establish a histological diagnosis. The four remaining cores should be snap frozen in liquid nitrogen within 30 minutes after biopsy and stored at -80°C. The biopsies should be transferred to the Francis Crick Institute on dry ice.

19.3.2. BASELINE BIOPSY OF METASTATIC SITES (OPTIONAL)

Biopsy of a metastatic site at baseline is optional, at the discretion of the treating clinician. As many tissue cores as practicable (maximum of five) from one needle puncture should be obtained. All tissue cores should be snap frozen and stored at -80°C until transfer to the Francis Crick Institute on dry ice.

Selected participating sites in London may be asked to place one of the metastatic biopsy samples into room temperature tubes containing culture medium for transportation to the Francis Crick Institute on the day of collection for the primary culture of malignant and stromal cells. Tubes and culture medium will be supplied by Francis Crick Institute and will be collected by their staff or by tissue collectors employed on the A-PREDICT trial.

19.3.3. PRIMARY TUMOUR TISSUE SAMPLE AT 8 WEEKS

Image guided percutaneous biopsy of the primary tumour should be performed eight weeks after axitinib treatment commenced (day 1 week 9). Five tissue cores should be obtained; one sample will be sent for paraffin embedding and analysis by the local pathologist and the remaining four cores should be snap frozen, stored at -80°C until transfer to the Francis Crick Institute on dry ice.

19.3.4. TUMOUR TISSUE SAMPLE AT PROGRESSION

As many tissue cores as practicable (maximum of five) from one needle puncture should be obtained, preferably from the site of progressive disease, at the time of tumour progression should be snap frozen and stored at -80°C until transfer to the Francis Crick Institute on dry ice. If it is not possible to sample the site of progression, biopsies of the primary tumour tissue should be taken, and processed using the same method as for the baseline and eight week samples.

19.3.5. NEPHRECTOMY SPECIMEN

Nephrectomy specimens if available should be dissected by the local pathologist to obtain sufficient material for routine diagnostic purposes. Following this, separate samples from the tumour and from the remaining normal kidney tissue should be taken for translational research studies. These tissues should be snap frozen in liquid nitrogen within 1 hour after the blood supply to the kidney has been interrupted and stored at -80°C at the local trial centre, until transferred to the Francis Crick Institute on dry ice.

Selected sites may be asked to place a nephrectomy sample into room temperature tubes containing culture medium for transportation to the Francis Crick Institute on the day of collection for primary culture of malignant and stromal cells. Tubes and culture medium will be supplied by Francis Crick Institute and will be collected by their staff or by tissue collectors employed on the A-PREDICT trial.

Trial centres should notify ICR-CTSU one week in advance of any planned surgery - see section 19.4 for details of expedited reporting mechanism.

19.3.6. PALLIATIVE SURGERY SPECIMENS

Tissue specimens from any palliative surgery should be examined by the local pathologist to obtain sufficient material for routine diagnostic purposes. Any additional tissue should be transferred to the Francis Crick Institute for translational research studies. These tissues should be snap frozen in liquid nitrogen immediately and stored at -80°C until transferred to the Francis Crick Institute.

Selected participating sites may be asked to place part of the specimen into room temperature Falcon tubes containing culture medium for transportation to the Francis Crick Institute on the day of collection for primary culture of malignant and stromal cells. Falcon tubes and culture medium will be supplied by Francis Crick Institute and will be collected by their staff or by tissue collectors employed on the A-PREDICT trial.

Trial centres should notify ICR-CTSU one week in advance of any planned surgery - see section 19.4 for details of expedited reporting mechanism.

19.3.7. PARAFFIN EMBEDDED TISSUE SECTIONS

Paraffin embedded core biopsies and nephrectomy specimens that are no longer needed by the local pathologist for diagnostic purposes may be requested and transferred to the Francis Crick Institute as required.

19.3.8. BLOOD AND URINE COLLECTION AND PROCESSING

Venous blood for biomarker analysis will be collected in EDTA tubes. **Two** tubes will be collected on day 1 week 1 prior to starting axitinib treatment, **two** tubes at the day 1 week 9 biopsy, and two at disease progression.

Immediate processing of blood samples must be undertaken locally. Detailed instructions for blood processing are contained in the laboratory manual.

Urine samples will also be collected on day 1 week 1, day 1 week 9, and at disease progression. Samples should be stored at -80°C at trial centres until transfer to Francis Crick Institute.

Each specimen container should be labelled as specified in the laboratory manual. Labels will be supplied by the ICR-CTSU as part of the sample collection kits.

19.3.9. STORAGE AND COLLECTION OF SAMPLES

Blood, urine and tissue samples should be stored at local trial centres in a -80°C freezer and transferred in batches when requested to the Francis Crick Institute on dry ice if not part of the fresh tissue for cell culture study.

19.3.10. TRANSLATIONAL SAMPLE SCHEDULE

Visit/Assessment	Within 21 days prior to registration	Pre-treatment day 1 week 1	Day 1 week 9	Disease progression
Percutaneous image guided biopsy of non-necrotic region of primary renal tumour (5 cores, 1 to be sent to pathology for paraffin embedding, 4 to be snap frozen in liquid nitrogen and stored at -80°C)	X		X	
Percutaneous image guided biopsy of one metastatic site (up to 5 cores to be snap frozen in liquid nitrogen and stored at -80°C) *(OPTIONAL).*	X			
Percutaneous image guided biopsy of site of progression, or if not possible, of non-necrotic region of primary renal tumour (up to 5 cores to be snap frozen in liquid nitrogen and stored at -80°C)				X
2 EDTA tube blood samples spun down to obtain serum (serum to be stored at -80°C)		X	X	X
Urine sample (1 container to be stored at -80°C)		X	X	X

19.4. SAMPLE TRACKING

Sites will be required to record the collection of participants' samples on an electronic reporting form which will enable tracking of samples by the Francis Crick Institute and ICR-CTSU

19.4.1. TRACKING OF BASELINE SAMPLES FOR INELIGIBLE PATIENTS

In order to minimise invasive procedures, patients will be consented for the trial prior to obtaining both the standard diagnostic biopsy sample and baseline translational study research biopsies. Patients will be asked to provide consent for the research samples to be sent to the Francis Crick Institute should histological examination of the diagnostic sample show that the patient is ineligible for A-PREDICT. Collection of these samples should be notified to the ICR Clinical Trials and Statistics Unit (ICR-CTSU) by telephoning:

020 8643 7150

09.00-17.00 (UK time) Monday to Friday

The following information will be required:

- Centre name

- Confirmation of written informed consent
- Patient's gender
- Patient's date of birth

This notification will allow these samples to be tracked by the Francis Crick Institute and ICR-CTSU.

19.5. EXPEDITED REPORTING OF FRESH TUMOUR TISSUE COLLECTION, PLANNED NEPHRECTOMY OR OTHER PALLIATIVE SURGICAL PROCEDURES

All participating sites must notify ICR-CTSU at least one week in advance of the date of planned nephrectomy or other palliative surgery.

Centres should notify ICR-CTSU of the planned procedures detailed above, by completing the A-PREDICT expedited notification of tissue collection form (included in laboratory manual) and faxing it to:

0208 722 4368

For the attention of the A-PREDICT Trial team

19.6. SAMPLE PROCESSING AT THE FRANCIS CRICK INSTITUTE (FORMERLY THE LONDON RESEARCH INSTITUTE)

19.6.1. CORE BIOPSY AND NEPHRECTOMY SPECIMENS

Processing of core biopsy, nephrectomy and surgical specimens will be conducted at the Francis Crick Institute. Microdissection of tumour samples will be performed to separate malignant cells from associated stromal components and RNA and DNA from each will be extracted immediately after dissection according to GLP standards.

All samples will be catalogued in an electronic database at the Francis Crick Institute. The time from core biopsy collection to snap freezing and from ischaemia to snap freezing for nephrectomy specimens will be recorded on a database. All tissues will be stored in an alarmed and locked -80°C freezer which is dedicated to the storage of clinical trial patient samples.

19.7. ANALYSIS OF TUMOUR TISSUES

Tumour tissue analysis aims to correlate changes in biomarkers with toxicity, response to axitinib treatment and survival.

The techniques below may be used to explore this endpoint and are based on the current literature. Equivalent novel methods and technologies might be used at the time of analysis.

19.7.1. RNA AND MIRNA EXPRESSION ANALYSIS

Total RNA from renal specimens will be isolated from tissue obtained before and after Axitinib exposure and at the time of tumour progression. The effects of Axitinib on changes in genome wide and targeted gene expression patterns in malignant cells and tumour stroma will be analysed by RNA expression analysis and the expression patterns of these tissues will be compared between

responding patients, those who achieve disease stabilization and those who progress despite Axitinib treatment.

19.7.2. TUMOUR DNA SEQUENCE AND COPY NUMBER ANALYSIS

Whole genome sequencing of tumour tissue DNA and RNA using deep sequencing technology) will also be conducted. Sequencing will include but not be restricted to regulators of VEGFR, PI3K, mTOR, S6K and VHL pathways including novel regulators of mTOR/S6K pathway signaling identified from functional genomic datasets to identify candidate genes associated with resistance and sensitivity prior to and after axitinib treatment**.** Tumours will also be profiled for chromosomal numerical heterogeneity status by FISH and for gene copy number variations

19.7.3. DATA ANALYSIS OF GENETIC HIGH-THROUGHPUT METHODS

The data from the high-throughput methods described above will be analysed by the bioinformatics group at the Francis Crick Institute. Pre-treatment expression signatures and changes in expression levels on treatment will be correlated with clinical response, primary resistance and to the development of secondary resistance to axitinib treatment as assessed by CT scanning. Gene specific quantitative rtPCR analyses will be used to validate expression data from the high-throughput assays and to correlate findings from whole genome RNAi analyses performed in renal cancer models in vitro.

19.7.4. TUMOUR IMMUNOHISTOCHEMISTRY AND IN SITU HYBRIDIZATION

Molecular analyses of any additional paraffin embedded tissue sections may be carried out to determine the effects of axitinib on changes in the phosphorylation status of proteins in the mTOR signaling pathway in tumour tissue (to include PTEN, p-AKT, p-PRAS40, p-70S6K, p-S6RP, p-4E-BP1) and to determine the effects of axitinib on changes in the levels of target genes and proteins in the VHL-HIF pathway in tumour tissue (to include VHL, HIF, VEGF family, GLUT-1). Additional pathways may be evaluated based on the contemporary literature at the time of analysis.

19.8. ANALYSIS OF BLOOD SAMPLES

One blood sample (taken at baseline) will be analysed for genomic DNA, and two blood samples taken at day 1 week 1, day 1 week 8 and disease progression will be analysed for circulating biomarkers, including circulating angiogenic markers, microRNA and tumour DNA.

Plasma levels of VEGF, PIGF, sVEGFR1-3 and new regulators of angiogenesis will be measured by ELISA analysis of plasma samples collected immediately before starting axitinib and on treatment. High-throughput deep-proteome analysis will be used to identify new protein biomarkers that predict axitinib sensitivity and resistance.

Total RNA from human blood will be isolated before and after axitinib exposure and RNA concentration will be quantified. Differential miRNA expression will be analysed and results will be compared with miRNA expression in matched tumour samples and data analysed in the Bioinformatics department at the Francis Crick Institute.

Circulating tumour DNA will be quantified to analyse tumour dynamics during axitinib treatment. Circulating cell-free DNA will be isolated from plasma samples after double centrifugation to remove any cellular components and debris and the amount of circulating DNA of mutated genes that were identified in the tumour DNA sequencing project will be quantified by real time PCR analysis and BEAM or by Solexa (Illumina, San Diego, USA) high throughput sequencing techniques.

Isolation and analysis of genomic DNA in parallel with tumour DNA will be important to validate tumour specific genomic copy number changes. Genomic DNA will be isolated by standard protocols from white blood cells that were extracted from peripheral blood by centrifugation.

The specific techniques which will be utilised are based on the current literature, but equivalent novel methods and technologies might be used at the time of analysis.