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

Summary

EudraCT number	2011-004562-16
Trial protocol	GB
Global end of trial date	28 February 2022

Results information

Result version number	v1 (current)
This version publication date	15 March 2023
First version publication date	15 March 2023

Trial information

Trial identification

Sponsor protocol code	ICR-CTSU/2011/10033

Additional study identifiers

ISRCTN number	ISRCTN72679844
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor Identification Number: CCR3587, ICR-CTSU Protocol Number: ICR-CTSU/2011/10033, REC reference: 12/LO/0639, IRAS: 98117

Notes:

Sponsors

Sponsor organisation name	The Institute of Cancer Research
Sponsor organisation address	15 Cotswold Road, London, United Kingdom, SM2 5NG
Public contact	Rebecca Lewis, The Institute of Cancer Research, 44 02087224081, apredict-icrctsu@icr.ac.uk
Scientific contact	Rebecca Lewis, The Institute of Cancer Research, 44 02087224081, apredict-icrctsu@icr.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2022
Global end of trial reached?	Yes
Global end of trial date	28 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does treatment with axitinib stop previously untreated widespread kidney cancer that can't be surgically removed from getting worse for at least 6 months?

Protection of trial subjects:

For trial entry and optional tissue donation, patients were given a verbal explanation, discussion and written information.
The Principal Investigator at each site was responsible for ensuring written informed consent was obtained for each patient.
Eligible patients were given as much time as they needed to consider and come to a decision about entering the trial, prior to giving consent for registration.
The patient information sheet, described fully which parties would have access to their identifiable personal information and patients were asked to give consent to this. The trial was overseen by an Independent Data Monitoring Committee, who reviewed the accumulating trial data and could recommend stopping the trial if there was any cause for concern about patient safety and if this were the case the patient's oncologist would be notified.

Background therapy:

Renal cell carcinoma (RCC) is diagnosed in around 8,500 patients and accounts for approximately 3% of malignant disease annually in the UK. 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. 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 and reported response rates to chemotherapy and hormonal agents 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.

Evidence for comparator:

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 and SouthWest Oncology Group 8949, 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.

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, 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, thyroid, and pancreatic cancers, and melanoma.

Actual start date of recruitment	01 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 65
Worldwide total number of subjects	65
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	36
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 10 October 2012 and 23 December 2016, 65 participants were registered into A-PREDICT from 11 UK hospitals.

Pre-assignment

Screening details:

Patients who met the eligibility criteria were recruited. Eligible patients had histologically confirmed metastatic renal cell carcinoma of predominant clear cell histology and who were not immediately clinically indicated for debulking nephrectomy (as judged by the treating clinician). Patients were over 18 with no prior systemic therapy.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Axitinib

Arm description:

All participants started open-label axitinib on 5mg dose taken orally, twice daily, until clinical benefit was no longer derived

Arm type	Experimental
Investigational medicinal product name	Axitinib
Investigational medicinal product code	
Other name	Inlyta
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were prescribed a starting dose of 5mg tablet BID. Patients who tolerated axitinib with no adverse events related to study drug above CTCAE grade 2 for a consecutive 2-week period could have their dose increased by one dose level to a maximum of 10 mg BID (unless the patient’s blood pressure [BP] was >150/90 mm Hg or the patient was receiving antihypertensive medication). If the patient received antihypertensive medication and a dose escalation was clinically indicated TMG approval was obtained for the proposed dose escalation. No patient receiving antihypertensive medication could have an axitinib dose escalation without prior TMG approval.

Number of subjects in period 1	Axitinib
Started	65
Completed	65

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial (overall period)

Reporting group description: -

Reporting group values	Overall Trial (overall period)	Total	
Number of subjects	65	65	
Age categorical			
Age at registration in years			
Units: Subjects			
40-49 years	8	8	
50-59 years	19	19	
60-69 years	26	26	
70+ years	12	12	
Age continuous			
Age at registration in years			
Units: years			
median	63.5		
inter-quartile range (Q1-Q3)	56.7 to 69.0	-	
Gender categorical			
Units: Subjects			
Female	22	22	
Male	43	43	
Histological type			
Units: Subjects			
Clear cell	62	62	
Clear cell and chromophobe	2	2	
Clear cell and sarcomatoid component	1	1	
Fuhrman grade			
Units: Subjects			
G1	2	2	
G2	26	26	
G3	21	21	
G4	2	2	
Unobtainable	14	14	
Motzer Score			
Units: Subjects			
Intermediate risk	50	50	
High risk	15	15	

Subject analysis sets

Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This population contains all people registered into the study (regardless of whether they were later found to be ineligible, a protocol deviator, never treated etc.).

Reporting group values	Intention to treat		
Number of subjects	65		
Age categorical			
Age at registration in years			
Units: Subjects			
40-49 years			
50-59 years			
60-69 years			
70+ years			
Age continuous			
Age at registration in years			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical			
Units: Subjects			
Female			
Male			
Histological type			
Units: Subjects			
Clear cell	62		
Clear cell and chromophobe	2		
Clear cell and sarcomatoid component	1		
Fuhrman grade			
Units: Subjects			
G1	2		
G2	26		
G3	21		
G4	2		
Unobtainable	14		
Motzer Score			
Units: Subjects			
Intermediate risk	50		
High risk	15		

End points

End points reporting groups

Reporting group title	Axitinib

Reporting group description:

All participants started open-label axitinib on 5mg dose taken orally, twice daily, until clinical benefit was no longer derived

Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This population contains all people registered into the study (regardless of whether they were later found to be ineligible, a protocol deviator, never treated etc.).

Primary: Proportion of patients free from disease progression

End point title	Proportion of patients free from disease progression[1]

End point description:

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.

End point type	Primary

End point timeframe:

6 months from the commencement of treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm study and no comparative analysis was performed, however the system expects at least 2 groups to be identified. All methods and options specified in the analysis section apply to statistical methods and summary measures to report and compare at least 2 independent groups, which is not the case in this single arm trial. There is no way of reporting one group inference and summary values without triggering an error or reporting inaccurate information.

End point values	Axitinib	Intention to treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65	65		
Units: Percentage				
number (confidence interval 58.5%)	58.5 (45.6 to 70.6)	58.5 (45.6 to 70.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response

End point title	Best overall response

End point description:

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.

End point type	Secondary

End point timeframe:

Best response as calculated while patients are on treatment.

End point values	Axitinib	Intention to treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65	65		
Units: Number				
CR	1	1		
PR	19	19		
SD	29	29		
PD	16	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

Progression-free survival (PFS) is 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 is used if patient has not progressed or died and PFS time for the patient is considered censored.

End point type	Secondary

End point timeframe:

6 months

End point values	Axitinib	Intention to treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65	65		
Units: Survival time				
number (confidence interval 63.1%)	63.1 (50.2 to 74.7)	63.1 (50.2 to 74.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

OS is defined as time from registration to death from any cause. Patients who have not been reported to have died are censored at last follow-up.

End point type	Secondary

End point timeframe:

Median survival time based on all follow-up available.

End point values	Axitinib	Intention to treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65	65		
Units: Months				
median (inter-quartile range (Q1-Q3))	19.7 (9.2 to 37.2)	19.7 (9.2 to 37.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients who undergo nephrectomy

End point title	Proportion of patients who undergo nephrectomy

End point description:

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

End point type	Secondary

End point timeframe:

Whilst patients are on treatment.

End point values	Axitinib	Intention to treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65	65		
Units: Percentage				
number (confidence interval 13.8%)	9 (6.5 to 24.7)	9 (6.5 to 24.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 28 days of the patient receiving study drug.

Adverse event reporting additional description:

Progression of the malignancy was not reported as a serious adverse event. Hospitalisation due to signs and symptoms of malignancy progression was not reported as a serious adverse event. Occurrences are counted as any subject reporting a particular AE at a visit where toxicity was assessed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Axitinib

Reporting group description:

This population contains all patients who received at least one dose of axitinib.

Serious adverse events	Axitinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 64 (40.63%)		
number of deaths (all causes)	62		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Chills				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	3 / 64 (4.69%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	3 / 64 (4.69%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	4 / 64 (6.25%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	4 / 64 (6.25%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	1 / 1			
Productive cough				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Mental disorder				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Investigations			
Blood calcium increased			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Wound dehiscence			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			

subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Thrombocytopenia				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	3 / 64 (4.69%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypophagia				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 64 (3.13%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Haematuria				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Nephrotic syndrome				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Urinary retention				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Adrenal insufficiency				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	4 / 64 (6.25%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Muscular weakness				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Infection				
subjects affected / exposed	2 / 64 (3.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumonia				
subjects affected / exposed	3 / 64 (4.69%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	2 / 64 (3.13%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				

Decreased appetite			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Hyponatraemia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Axitinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 64 (100.00%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	19		
Hypertension			
subjects affected / exposed	60 / 64 (93.75%)		
occurrences (all)	881		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	11 / 64 (17.19%)		
occurrences (all)	15		
Fatigue			
subjects affected / exposed	61 / 64 (95.31%)		
occurrences (all)	651		
Mucosal inflammation			
subjects affected / exposed	32 / 64 (50.00%)		
occurrences (all)	157		

Oedema peripheral subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 9		
Pain subjects affected / exposed occurrences (all)	11 / 64 (17.19%) 50		
Pyrexia subjects affected / exposed occurrences (all)	10 / 64 (15.63%) 13		
Reproductive system and breast disorders Vaginal haemorrhage subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 15		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	25 / 64 (39.06%) 105		
Dysphonia subjects affected / exposed occurrences (all)	26 / 64 (40.63%) 190		
Dyspnoea subjects affected / exposed occurrences (all)	29 / 64 (45.31%) 145		
Epistaxis subjects affected / exposed occurrences (all)	9 / 64 (14.06%) 22		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	17 / 64 (26.56%) 99		
Mood altered subjects affected / exposed occurrences (all)	6 / 64 (9.38%) 9		
Investigations Alanine aminotransferase increased			

subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	8		
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 64 (15.63%)		
occurrences (all)	22		
Blood creatinine decreased			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	11		
Blood creatinine increased			
subjects affected / exposed	8 / 64 (12.50%)		
occurrences (all)	23		
Blood lactate dehydrogenase increased			
subjects affected / exposed	7 / 64 (10.94%)		
occurrences (all)	25		
Blood magnesium decreased			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	13		
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 64 (12.50%)		
occurrences (all)	26		
Lymphocyte count decreased			
subjects affected / exposed	11 / 64 (17.19%)		
occurrences (all)	49		
Platelet count increased			
subjects affected / exposed	6 / 64 (9.38%)		
occurrences (all)	8		
Prothrombin time prolonged			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	9		
Weight decreased			
subjects affected / exposed	28 / 64 (43.75%)		
occurrences (all)	166		
Injury, poisoning and procedural complications			

Wound complication subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 4		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Neuralgia subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	 12 / 64 (18.75%) 44 28 / 64 (43.75%) 167 16 / 64 (25.00%) 35 5 / 64 (7.81%) 7 5 / 64 (7.81%) 8 6 / 64 (9.38%) 28		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 13 / 64 (20.31%) 24		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth	 26 / 64 (40.63%) 131 27 / 64 (42.19%) 189 38 / 64 (59.38%) 434		

subjects affected / exposed	6 / 64 (9.38%)		
occurrences (all)	7		
Dyspepsia			
subjects affected / exposed	15 / 64 (23.44%)		
occurrences (all)	56		
Mouth ulceration			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	14		
Nausea			
subjects affected / exposed	38 / 64 (59.38%)		
occurrences (all)	181		
Oral pain			
subjects affected / exposed	6 / 64 (9.38%)		
occurrences (all)	25		
Stomatitis			
subjects affected / exposed	22 / 64 (34.38%)		
occurrences (all)	90		
Vomiting			
subjects affected / exposed	24 / 64 (37.50%)		
occurrences (all)	79		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 64 (12.50%)		
occurrences (all)	12		
Dry skin			
subjects affected / exposed	20 / 64 (31.25%)		
occurrences (all)	54		
Night sweats			
subjects affected / exposed	7 / 64 (10.94%)		
occurrences (all)	31		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	23 / 64 (35.94%)		
occurrences (all)	217		
Pruritus			

subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	10		
Rash			
subjects affected / exposed	20 / 64 (31.25%)		
occurrences (all)	85		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	38 / 64 (59.38%)		
occurrences (all)	234		
Renal pain			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	11		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	4		
Hypothyroidism			
subjects affected / exposed	28 / 64 (43.75%)		
occurrences (all)	194		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 64 (35.94%)		
occurrences (all)	204		
Back pain			
subjects affected / exposed	37 / 64 (57.81%)		
occurrences (all)	236		
Bone pain			
subjects affected / exposed	7 / 64 (10.94%)		
occurrences (all)	16		
Flank pain			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	7		
Joint swelling			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	17		
Muscle spasms			

subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	4		
Muscular weakness			
subjects affected / exposed	20 / 64 (31.25%)		
occurrences (all)	56		
Musculoskeletal chest pain			
subjects affected / exposed	9 / 64 (14.06%)		
occurrences (all)	16		
Musculoskeletal pain			
subjects affected / exposed	13 / 64 (20.31%)		
occurrences (all)	71		
Musculoskeletal stiffness			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	8		
Myalgia			
subjects affected / exposed	9 / 64 (14.06%)		
occurrences (all)	33		
Pain in extremity			
subjects affected / exposed	21 / 64 (32.81%)		
occurrences (all)	101		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	7 / 64 (10.94%)		
occurrences (all)	13		
Nasopharyngitis			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	4		
Urinary tract infection			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	10		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	45 / 64 (70.31%)		
occurrences (all)	243		
Hypercalcaemia			

subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	7		
Hyperglycaemia			
subjects affected / exposed	6 / 64 (9.38%)		
occurrences (all)	41		
Hypoalbuminaemia			
subjects affected / exposed	13 / 64 (20.31%)		
occurrences (all)	34		
Hyponatraemia			
subjects affected / exposed	6 / 64 (9.38%)		
occurrences (all)	17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2012	Protocol amendment to trial assessments and drug dispensing schedule. An additional pregnancy test was included to be conducted within 3 days prior to commencing treatment. The timeframe for stopping axitinib prior to day 1 week 9 biopsy was extended from 7 days to 5-7 days. Timelines for response assessment and biopsy when the patient stopped trial treatment were inserted. The schedule of assessments was amended in line with these changes. A "Subsequent Therapy" section was added confirm that "Participants for whom treatment is discontinued should be treated according to clinical circumstances and should be managed at the local clinician's discretion." Addition of new participating centres.
25 January 2013	Amendment to the Patient Information Sheet and Consent Form relating to the frequency of hospital visits and details regarding participant biopsies. Addition of new participating centres.
25 October 2013	The study Reference Safety Information (RSI) had been updated to the Summary of Medical Product Characteristics (SmPC), and any reference to the Investigator Brochure (IB) in the protocol had been replaced by SmPC. The protocol was revised throughout for consistency with the SmPC. The protocol was updated to state that eligible patients included those with unresectable primary tumours, those with a large metastatic burden or those unfit for nephrectomy. Further changes were included to the timing of scheduled assessments and guidance around treatment interruptions. Addition of new participating centres and a change in Principal Investigator at a participating centre.
16 May 2014	The protocol was amended to clarify that where a patient received antihypertensive medication and a dose escalation was clinically indicated, this was permitted with TMG approval on a case-by-case basis. The urinalysis section of the protocol was amended allow an additional method in the assessment for proteinuria. Centres may use urinary protein:creatinine ratio (PCR).
13 May 2015	The protocol was amended to note the London Research Institute (LRI) had become part of the Francis Crick Institute (FCI); the addition of an exploratory endpoint to investigate any effect of treatment on the extent of inferior vena cava (IVC) venous tumour thrombus (VTT); provision to allow the use of prohibited medications in exceptional circumstances if approved by the Chief Investigator, and a minor correction to the translational sample schedule. Change of principal investigator at an existing site.
26 November 2015	The protocol inclusion criteria were updated to state that adequate organ function can be defined by an AST or ALT reading rather than requiring both and that the baseline systolic BP readings must be ≤150 mm Hg in accordance with the current SmPC. Change in Principal Investigator at an existing centre.

08 November 2016	The protcol exclusion criteria were update to include known galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption. Guidance relating to dose modification for axitinib related adverse events; dose reduction for proteinuria; and concomitant therapy were added to the protocol in line with the new version of Reference Safety Information. Changes to dose reduction guidance for hypertension for consistency with systolic pressure guidance Collection of fresh tissue for cell culture from London sites removed as no longer required The Patient Information Sheet's Serious and Common side effects section was revised in light of updated Reference Safety Information.
24 January 2017	Closure to recruitment. A-PREDICT closed to recruitment on 23/12/2016 following feedback from the Independent Data Monitoring and Steering Committee, who met on the 01/12/2016. The IDMSC reviewed the number of A-PREDICT participants progression free at week 24 and advised recruitment should close as no further participants were required to assess the primary objective, 65 participants were recruited in total. the original sample size was 99 participants. The recommendation to close to recruitment was not based on any safety reasons. Participants receiving treatment at the time of closure continued on treatment as per protocol.
02 November 2018	Protocol amendment detailing the introduction of a new axitinib supply process following transfer of participants to commercial supply after expiration of the existing trial supply on 31/11/2018.
12 June 2019	Update to reference safety information. The patient information sheet was updated in line with the new reference safety information and to include statement to explain translational analysis of samples collected in A-PREDICT may occur outside of the Francis Crick Institute either in the UK or abroad.
02 June 2020	The reference safety information was updated due to the release of the axitinib (Inlyta) SmPC in which cholecystitis had been added as a common adverse event. The protocol follow up schedule had been rationalised for patients who had been on treatment for a considerable amount of time as four weekly assessment was no longer clinically required after this duration on treatment. Hospital visits were aligned with scan frequency for the convenience of participants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported