AXMUS-C CLINICAL TRIAL PROTOCOL

A PHASE II DOUBLE BLIND, RANDOMISED CONTROLLED TRIAL OF VEGF INHIBITOR AXITINIB MONOTHERAPY WITH EARLY DYNAMIC CONTRAST ENHANCED ULTRASOUND MONITORING IN CHEMOREFRACTORY THIRD LINE METASTATIC COLORECTAL CANCER

Study Summary:

Compound:	AG-013736
Compound Name:	Axitinib
REC reference:	12/LO/0066
EudraCT number:	2011-002598-49
Authors:	Brahman Dharmarajah, Edward Leen, Ankur Thapar, Beate Poppinga-Scholz, Harpreet Wasan
Academic Sponsor:	Imperial College, London
Sponsor reference:	CRO1885
Grant Code:	31605
Funder:	**Investigator initiated - Grant from Pfizer**
Funder reference:	WS913975
Principal Investigator:	Harpreet Wasan
Version:	1.1
Date:	14/12/2011

Trial Summary

Objectives of AXMUS-C Phase II Randomised Controlled Pilot study in colorectal cancer

Overall aims: Axitinib has been used in the Phase II and III setting in many cancers, with an adequate safety profile. Its role in the treatment of colorectal cancer as monotherapy has yet to be defined.

- To evaluate the efficacy of Axitinib (a VEGF inhibitor) monotherapy in third-line metastatic colorectal cancer and improve clinical outcomes in chemotherapy- refractory metastatic CRC

- To test the potential for dynamic contrast-enhanced ultrasound as a potential novel imaging biomarker of early response against RECIST criteria

Primary objective of trial

- To demonstrate a progression-free survival to Axitinib monotherapy in refractory (to all known conventional treatments) metastatic colorectal cancer

Secondary objectives of trial

- To assess the correlation in patients with a confirmed vascular response (as evaluated by a greater than 20% reduction in CEPHI at 2 weeks).
    - This assessment will be done by separating out the RECIST-progressors (non-responders) who can also be detected by CEPHI at 2 weeks, and comparing this with RECIST responders (CR+PR+SD). The patients receiving Placebo will be included in this analysis.
    - To demonstrate the value of CEPHI as an early imaging selection biomarker of non-response (or response) in patients who have had at least 4 weeks of study treatment.

- To compare overall survival between the treatment and placebo arms
- To compare the overall RECIST response rate between the treatment and placebo arms
- To compare and correlate the 2 week CEHPI and 8 week RECIST response rates.
- To compare the median overall survival of patients receiving Axitinib who develop new diastolic hypertension (>90mmHg) with those that do not (in either/or the blinded placebo group or treatment group combined)
- To identify if CEHPI will function as a non-invasive correlative biomarker of Axitinib pharmacokinetics (PK) and help minimise toxicity and identify responders
- Toxicity (CTC) i for the treatment and placebo arms

Study Design

A Phase II, double-blind, 2 arm pilot randomised placebo controlled trial. 50 patients will be randomised 2:1 to Axitinib or placebo.

Main Inclusion criteria: Chemo-refractory third-line metastatic CRC with US-assessable liver or other abdominal metastases that can have a baseline DCEUS baseline measurement.

Arm A: Axitinib monotherapy started in all patients at 5mg bd, and increased fortnightly by a dose level (See Table 4) as tolerated to a maximum dose of 10mg bd.

Arm B: Placebo at 2:1 ratio to treatment

Follow up: *Optional* visit at 48-72 hours post first dose for measurement of temperature, oxygen saturations, blood pressure and CEHPI. Outpatient monitoring at 2 weeks and 4 weeks post first dose and at 4 week intervals thereafter which will include medical history and examination, measurement of temperature, oxygen saturations and blood pressure, urinalysis and blood tests including GI profile and VEGF-PK samples. RECIST restaging at 8 weeks and at 8 weekly intervals thereafter. CEHPI will be performed at baseline, optionally at 48-72 hours, 2 weeks and 8 weeks for assessment of differential blood supply. At 8 weeks, after tumour CT RECIST assessments, conventional responders (CR/PR/SD) continue monotherapy. In non-responders (PD), monotherapy can be continued if patient chooses to continue and if tolerated.

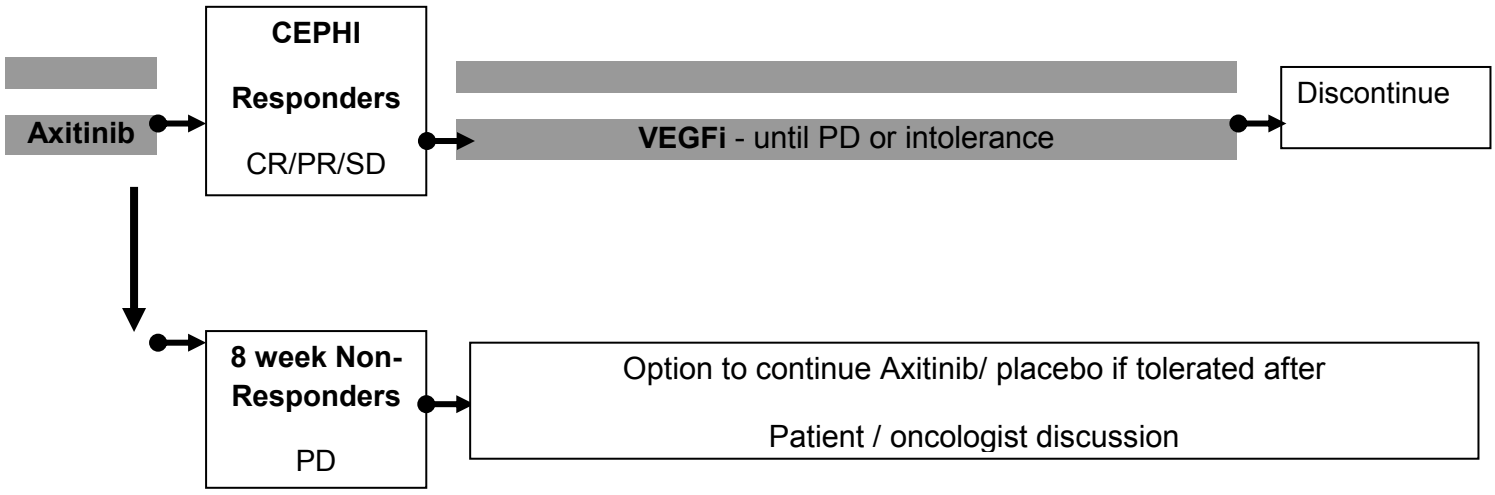


Figure 1: Protocol for responders and non-responders to Axitinib at 8 week RECIST evaluation.

Trial Treatment

Axitinib or placebo will be administered, twice daily (BD) on a continuous daily dosing schedule, to patients randomised to Arm A or Arm B, respectively**.** The starting dose will be 5mg bd. Doses should be taken with food as close to 12 hours apart as possible and at approximately the same times each day on a continuous schedule. Patients who tolerate Axitinib/placebo with no adverse events related to Axitinib/placebo above CTCAE Grade 2 and BP <150/90mmHg for a consecutive 2-week period should have their dose increased by one dose level (see 5.8 Dosing). The clinical judgment of the treating physician should be exercised when titrating Axitinib/placebo dose. In cases where it is not obvious whether Axitinib/placebo is a contributor to adverse event(s), dose titration will remain at the investigator's discretion.

The study treatment may be permanently discontinued upon progression of disease, occurrence of unacceptable toxicity, withdrawal of patient consent, or other withdrawal criterion is met. However, patients who have progressive disease (PD) but have experienced clinical benefit from Axitinib or placebo treatment will be eligible for continued treatment provided that the treating physician has assessed the risk/benefit of taking such an approach and no alternative treatment is available.

Patients who require different systemic cancer treatment from what they were assigned at randomization must be withdrawn from the study and followed as described below. After discontinuation of study treatment and the mandated 28-day follow-up period, patients will continue to be followed in order to collect information on further anti-tumour therapy and survival. A safety committee will convene every 3 months to review adverse events and determine the safety in the study.

	Screening (Day -28 to day 0)	Predose Day 1	48-72 hours	2 weeks	4 weeks	8 weeks	Monthly	End of study	28 days post-final dose
Informed consent	✓								
Medical history / symptoms	✓			✓	✓	✓	✓	✓	✓
BMI & ECG	✓					✓		✓	
Clinical exam	✓	✓		✓	✓	✓	✓	✓	✓
Temperature, pulse, $Sa0_2$,blood pressure	✓	✓	✓ (Optional)	✓	✓	✓	✓	✓	✓
Blood tests (GI profile)	✓	✓		✓	✓	✓	✓	✓	✓
Urinalysis	✓	✓		✓	✓	✓	✓	✓	✓
Thyroid function blood test		✓		✓	✓	✓	✓	✓	✓

Schedule of Activities

CEHPI ultrasound		✓	✓ (Optional)	✓		✓			
CT RECIST Staging	✓ (if last CT scan >28 days since randomization date)					✓ and 8 weekly thereafter		✓	
PK				✓	✓	✓		✓	✓

Table of Contents

1. INTRODUCTION 11
1.1. Indication 11
1.2. Background and Rationale 11
1.3. Axitinib Molecular Formula and Molecular Activity 14
1.4 Side effect profile 16
2. STUDY OBJECTIVES AND ENDPOINTS 19
2.1. Objectives 19
2.2 ENDPOINTS 20
Primary Endpoints 20
Exploratory / Safety Endpoints 20
3. Study Design 21
4. Subject Selection 23
4.1. Inclusion criteria 23
4.2 Exclusion criteria 23
4.3. Life Style Guidelines 25
5. Study Procedures 26
5.1. Allocation to Treatment 26
5.2 Randomisation 26
5.3 Blinding 26
5.4. Drug Supplies (Axitinib and Placebo) 26
5.5 Formulation and Packaging 26
5.6 Preparation and Dispensing 26
5.7 Administration 27
5.8 Dosing 27
5.9 Dose Interruption and Reduction 27
5.10 Management of Axitinib-Related Adverse Events 28
5.11 Axitinib/Placebo Dose Reduction for Hypertension 27
5.12 Axitinib/Placebo Dose Reduction for Proteinuria 29
5.13. Axitinib/Placebo Dose Interruption for Surgery or Surgical Procedures 31
5.14 Compliance 31
5.15 Drug Storage and Drug Accountability 31

5.16 Concomitant Medication(s) 32
5.17 Axitinib/Placebo 32
5.18 Salvage Therapy 34
6. Study Procedures 35
6.1 Screening 35
6.2 Study Period 35
6.3 End of Treatment 36
6.4 Subject withdrawal 37
6.5 Follow Up Visits 37
6.5.1. Additional Follow Up Visits 38
6.6. Survival Follow-up 38
7. Assessments 39
7.1. Efficacy Assessment 39
7.2. Physical Examination 41
7.3 Blood Pressure Assessments 41
7.4. Urinalysis 41
7.5. Haematology 41
7.6. Biochemistry 42
7.7. Thyroid Function Tests 42
7.8 Contrast Enhanced Hepatic Perfusion Index 42
7.9 Axitinib Pharmacokinetic Assessments 42
7.9.1. Collection, Processing, Storage and Shipment of Pharmacokinetic Samples 43
8. Adverse Event Reporting 44
8.1 Adverse Events 44
8.2. Reporting Period 44
8.3. Definition of an Adverse Event 44
8.4. Abnormal Test Findings 45
8.5. Serious Adverse Events 46
8.6. Hospitalisation 46
8.7. Severity Assessment 47
8.8. Causality Assessment 47
8.9. Exposure In Utero 47
8.10. Withdrawal Due to Adverse Events (See also Subject Withdrawal) 48
8.11. Eliciting Adverse Event Information 49

8.12. Reporting Requirements 49
8.12.1 Serious Adverse Event Reporting Requirements 49
8.12.2. Non-Serious Adverse Event Reporting Requirements 49
8.13. Suspected Unexpected Serious Adverse Reaction (SUSAR) 50
9. Statistical Analysis 52
9.1 Size of treatment effect 51
9.2 Statistical analysis plan 52
9.3 Pharmacokinetic analysis 52
9.4 Safety Analysis 52
9.5 Analysis of clinical laboratory data 52
9.6 Concomitant medications 53
10. QUALITY CONTROL AND QUALITY ASSURANCE 53
11. DATA HANDLING AND RECORD KEEPING 53
11.1. Case Report Forms / Electronic Data Record 53
11.2. Record Retention 54
12. ETHICS 54
12.1. Independent Ethics Committee & NHS R&D approval 54
12.2. Ethical Conduct of the Study 54
12.3. Subject Information and Consent 55
12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH Good 55
13. DEFINITION OF END OF TRIAL 55
13.1. End of Trial 55
14. SPONSOR DISCONTINUATION CRITERIA 55
5. PUBLICATION OF STUDY RESULTS 56
15.1. Communication of Results by Pfizer 56
15.2. Publications by Investigators 57
16. References 58
Appendix 1 Required laboratory tests 59
Appendix 2 Patient Information Sheet ..... 60_Toc297397325
Appendix 3 Informed Consent Form 72
Appendix 4 GP letter 73
Appendix 5 Liver Ultrasound Protocol 75
Appendix 6 RECIST Tumour Assessment Criteria (Version 1.1) 77

Appendix 7 ECOG Performance Status 831

Appendix 8 Pfizer Reportable Event Cover Sheet 842

REPORTABLE EVENT COVER SHEET 843

1. INTRODUCTION

1.1. Indication

Patients with metastatic colorectal carcinoma after failure of at least two previous chemotherapy regimens, defining the population as 'Chemo-refractory'

1.2. Background and Rationale

Colorectal cancer is the third most common cancer in the UK and the second most common cause of cancer death with an average 5 year survival of 50%[1] ENREF 6. The age standardised European incidence is 46 cases per 100, 000 people. The incidence of liver metastases is approximately 15% in contemporary studies. In the presence of liver metastases the 5-year survival rate falls to 3-7% on conventional therapy[2 3]. There is thus a pressing need to find new chemotherapeutic strategies for this common cause of cancer death.

The use of angiogenesis inhibition in cancer has a logical scientific basis with strong evidence of rapid normalisation of abnormal tumour vasculature, and reduction of tumour interstitial pressures. Although pre-clinically the combination of angiogenesis inhibitors with cytotoxic chemotherapy had shown additive efficacy, this was not necessarily synergistic in patient settings. In clinical trials, initial excitement that Vascular Endothelial Growth Factor Inhibitors (VEFGi) with combination cytotoxic chemotherapy was a correct paradigm shift was subsequently not borne out. There is now significant doubt that the benefits of combined cytotoxic and angiogenesis inhibition are marginal at best, in the current strategies employed. The design of recent and current randomized phase II and III trials does *not* appear to reflect the optimal potency of VEGF inhibition strategies as suggested by the pre-clinical models.

In colorectal cancer, the pivotal registration VEFGi study of Hurwitz ENREF 1 now looks increasingly aberrant, as subsequent studies have invariably been negative[4]. The inhibition of angiogenesis with Bevacizumab, (VEGF-binding antibody) combined with IFL chemotherapy (called the Saltz regimen: irinotecan/bolus 5-FU /leucovorin, is now considered an *inferior* regimen) improved median survival from 15 months to 20 months when used as first line therapy. Indeed currently, no oral tyrosine kinase inhibitor (TKI) with VEGF inhibitory activity has been able to demonstrate clinical efficacy in any line of treatment, in combination with cytotoxic chemotherapy in terms of overall survival or response by RECIST criteria ENREF 2.

The addition of Bevacizumab to the FOLFOX regimen has shown marginal PFS benefits (NO16966 study: less than one month advantage in the FOLFOX comparison, and less than 1.5 months in the XELOX arms (8 to 9.4mths)). Many health cost-effectiveness analyses including the UK National Institute for Clinical Excellence, have questioned the clinical value of these marginal benefits, in the absence of clear survival or response benefits.

In second line, again no overall survival benefit has been seen, but of underestimated importance, was that a third arm of Bevacizumab monotherapy had an overall survival equivalent to the control arm of FOLFOX4 (a standard of care), although the classical response rate to monotherapy was only 3.3%. Similarly designed randomised trials with combination FOLFIRI or FOLFOX and oral TKI's have almost all had premature closure, failing to meet their primary endpoints (including combinations with Sunitinib, AZ2171 and Sorafenib). There is also a suggestion from these trials that there may be a negative interaction with oxaliplatin based regimens specifically. Furthermore, the toxicity profiles of TKIs in combination with chemotherapy have constantly led to the question of whether the dosing for optimal efficacy versus toxicity has ever been achieved.

There is substantial emerging evidence that the correct dosing of these drugs is currently poorly managed and that patients on lower doses than suggested by conventional parameters, do not appear to be compromised for efficacy ENREF 3. Intermittent dosing has also been proposed as one method of optimisation and in the pivotal Sunitinib registration renal study the dose scheduling of 4 weeks on, 2 weeks off was highly effective.

The basic science of VEGF inhibitors suggests significant activity on normalising aberrant tumour vasculature.

The negative current clinical implications must necessarily lead to a rethink of the best way to clinically utilise and optimise the VEGF-inhibitor strategies. Previous work ENREF 4 has consistently shown that VEGF inhibitors as monotherapy, substantially change the tumour microenvironment and may within a period of days to weeks, normalise the vasculature and improve tumour access for sequential cytotoxic drugs[5]. Improved tissue hypoxia, which is a known chemo-resistant factor, may further augment these effects.

In monotherapy, VEGF inhibitors have clearly demonstrated significant survival benefits in other cancers. This is clinically significant efficacy *independent* of combinations with cytotoxic chemotherapy. Examples include:-

i) Sunitinib in renal cell carcinoma, pancreatic neuroendocrine tumours (and 2nd line in Imatinib-refractory GISTs). In phase II studies Sunitinib monotherapy has also demonstrated significant benefits in HCC with evidence of tumour necrosis.
ii) Sorafenib in HCC and renal cancer
iii) Emerging evidence in a maintenance monotherapy setting: Bevacizumab in first-line CRC after 3 months of cytotoxic chemotherapy and similarly in advanced ovarian cancer appears beneficial.

Thus in at least three diseases which are renowned for their severe chemotherapy and radiotherapy resistance, monotherapy with an inhibitor of multiple receptor tyrosine kinases pathways has radically changed the outlook for patients.

In colorectal cancer (CRC), the lack of classical responses has prompted the exploration of VEGF inhibitors such as Sunitinib in monotherapy. The clinical evidence means that we should be exploring how to use these drugs in novel ways. Indeed, the efficacy of single agent Sunitinib in chemorefractory CRC has been investigated in a Phase 2 study (A6181003), where there appeared to be stabilising activity and additionally a small subset of patients went on to respond. In this study, 84 patients were enrolled, 43 with prior Bevacizumab and 41 without prior Bevacizumab treatment. 82 patients were actually treated with Sunitinib and comprised the intention-to-treat population (1 patient in each cohort discontinued the study before receiving treatment). Overall, 67 (82%) patients discontinued the study due to disease progression, 8 (10%) due to adverse events, 1 (1%) was lost to follow-up, and 5 (6%) withdrew consent. One patient completed the study (1 year of therapy). In the analysis of the primary endpoint – overall response rate (ORR) - only 1 patient with prior Bevacizumab therapy had a confirmed partial response; twenty-four patients (29%; 10 [24%] with and 14 [35%] without prior Bevacizumab) had a best response of stable disease – among those, 2 (4.8%) with and 11 (27.5%) without prior Bevacizumab experienced stable disease for ≥22 weeks. Although Sunitinib failed to show significant classical responses in this population of heavily pretreated patients, an encouraging survival of 10 months was observed amongst Bevacizumab-naïve patients. This survival rate along with Sunitinib's mechanism of action and acceptable safety profile suggest that further investigation of Axitinib or similar drugs is warranted. Indeed, although cross trial comparisons are difficult: 10 months is as good as the Bevacizumab monotherapy arm in the second-line Bevacizumab naive E3200 study _ENREF_5.

Early Biomarkers of response are needed to rapidly select responders and help design new paradigms of clinical benefit.

The lack of validated and reproducible VEGF response biomarkers makes study of the optimal use of VEGF inhibitors time consuming for conventional RECIST end-points. We have developed a simple technique using differential liver blood flow assessments using microbubble (dynamic contrast-enhanced ultrasound) for liver tumours (primary and secondary) which appears promising[6]. This imparts information akin to dynamic contrast-enhanced MRI, but is cheaper, portable and much easier to perform serially. Measuring perfusion characteristics across individual liver lesions has problems with reproducibility and a bias towards larger, more visible lesions[7]. This is the result of liver including metastases having a dual blood supply with dynamic shifts in differential distribution between the metastases. To overcome this we have developed summation technology across the whole liver, measuring the ratios of arterial to portal venous flow _ENREF_9. This is termed the Contrast Enhanced Hepatic Perfusion Index (CEHPI). This is able to analyse differential blood flow in liver metastases that are responding and also detect differences in the distributable flow from the portal vein and hepatic artery. It is known that the neo-angiogenesis that supports the growth of malignant tumours in the liver, preferentially sources this from the hepatic artery (as opposed to the portal vein, which is the dominant source of blood to normal liver parenchyma). We have preliminary data that suggests that this trend is reversed towards normal liver portal venous flow in responding tumours with both cytotoxic chemotherapy and VEGF inhibitors including Bevacizumab.

1.3. Axitinib Molecular Formula and Molecular Activity

Axitinib, a substituted indazole derivative, is an oral, potent, and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3.

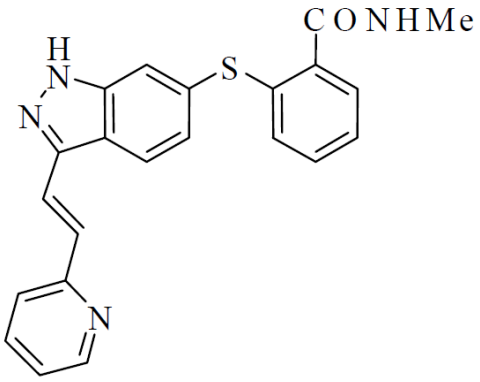


Figure 2: The molecular formula of Axitinib is $C_{22}H_{18}N_4OS$. It has a molecular weight of 386.47. The chemical name is N-Methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide.

Phase 2 studies with axitinib are ongoing or completed in various tumour types, including metastatic breast cancer (Protocol A4061010), non-small cell lung cancer (Protocol A4061011), cytokine-refractory renal cell carcinoma (RCC; Protocol A4061012, A4061035), radioiodine [131I]-refractory thyroid cancer (Protocol A4061014), malignant melanoma (Protocol A4061015), advanced pancreatic cancer (Protocol A4061016), colorectal cancer (CRC; Protocol A4061020, A4061034), sorafenib-refractory RCC (Protocol A4061023), iodine and doxorubicin-refractory thyroid cancer (Protocol A4061027), and non-small cell lung cancer (NSCLC; Protocol A4061030, A4061038, A4061039). A pivotal Phase 3 study in advanced pancreatic cancer (Protocol A4061028) was terminated early for futility.

Retrospective analyses of five AG-013736 Phase 2 studies across multiple tumour types (RCC, melanoma, NSCLC, and thyroid cancer) demonstrated that patients who developed at least one in-clinic measurement of dBP >90 mmHg at any point during treatment had significantly better clinical outcomes for OS (30.1 vs 10.2 months; hazard ratio [HR]=0.546; $p<0.001$), PFS (13.1 vs 5.8 months; HR=0.42; $p<0.001$), and ORR (43.9% vs 12.0 %; $p<0.001$). Figure 2: below shows the association between transient dBP > 90 mmHg with longer median OS.

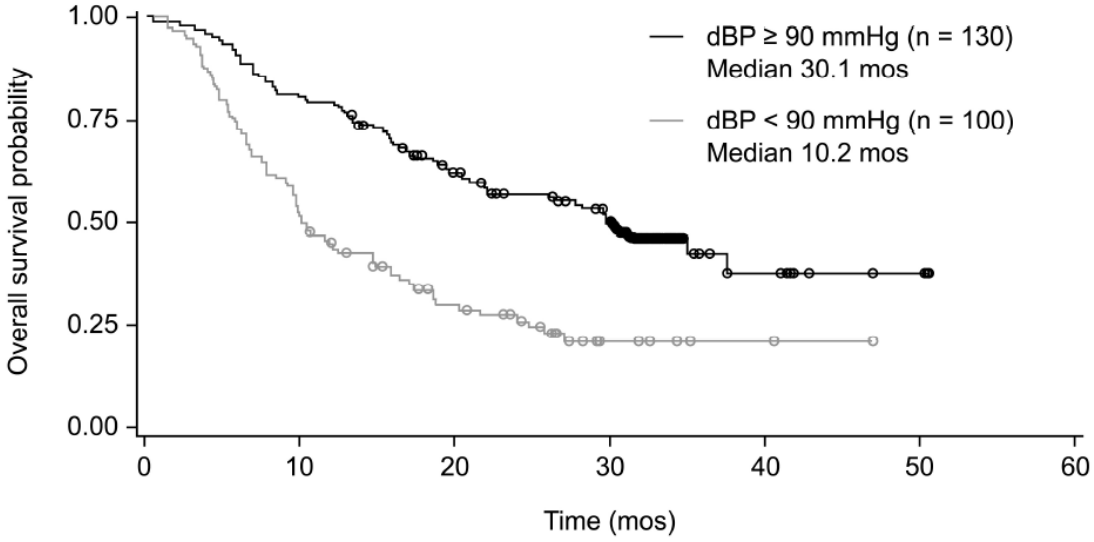


Figure 2: Association of new diastolic hypertension (>90mmHg) with improved median survival.

1.4 Side effect profile

As of June 3, 2009, human safety data were available for 2564 subjects, including 2175 patients with cancer and 389 healthy volunteers. The data from 364 subjects with solid malignant tumours treated with single-agent Axitinib are presented in the table below:

	Solid Tumor Single Agent (N=128)		**Breast Cancer Combination[a] (N=77)**		**AML/MDS Single-Agent (N=12)**		**Total (N=217)**	
MedDRA Preferred Term	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Fatigue	70 (55)	16 (13)	32 (42)	8 (10)	9 (75)		111 (51)	24 (11)
Diarrhoea	49 (38)	9 (7)	39 (51)	7 (9)	10 (83)	1 (8)	98 (45)	17 (8)
Nausea	56 (44)		34 (44)	1 (1)	6 (50)		96 (44)	1
Hypertension	56 (44)	22 (17)	19 (25)	5 (6)	5 (42)	4 (33)	80 (37)	31 (14)
Anorexia	40 (31)	4 (3)	25 (32)	1 (1)	2 (17)		67 (31)	5 (2)
Constipation	35 (27)	1 (1)	24 (31)		2 (17)		61 (28)	1
Dyspnoea	35 (27)	8 (6)	21 (27)	3 (4)	4 (33)	1 (8)	60 (28)	12 (6)
Headache	30 (23)	3 (2)	24 (31)	1 (1)	3 (25)		57 (26)	4 (2)
Vomiting	28 (22)		23 (30)	3 (4)	3 (25)		54 (25)	3 (1)
Stomatitis	17 (13)	5 (4)	28 (36)	7 (9)	4 (33)		49 (23)	12 (6)
Arthralgia	29 (23)	4 (3)	19 (25)	1 (1)			48 (22)	5 (2)
Cough	24 (19)	3 (2)	20 (26)		4 (33)		48 (22)	3 (1)
Hoarseness	31 (24)		6 (8)		9 (75)		46 (21)	
Pain in limb	30 (23)	3 (2)	14 (18)	2 (3)			44 (20)	5 (2)
Abdominal pain	20 (16)	3 (2)	21 (27)	2 (3)	2 (17)	1 (8)	43 (20)	6 (3)
Weight decreased	31 (24)	4 (3)	7 (9)	1 (1)	2 (17)		40 (18)	5 (2)
Neutropaenia			37 (48)	31 (40)			37 (17)	31 (14)
Dyspepsia	24 (19)	1 (1)	12 (16)				36 (17)	1
Back pain	18 (14)	4 (3)	13 (17)	3 (4)	4 (33)		35 (16)	7 (3)
Alopecia	3 (2)		32 (42)	4 (5)			35 (16)	4 (2)
Myalgia	16 (13)	3 (2)	18 (23)	1 (1)			34 (16)	4 (2)
Mucosal inflammation	7 (5)		22 (29)	4 (5)	4 (33)	1 (8)	33 (15)	5 (2)
Epistaxis	8 (6)		21 (27)		2 (17)		31 (14)	
Rash	14 (11)		13 (17)		4 (33)		31 (14)	
Anaemia	12 (9)	4 (3)	16 (21)		2 (17)	2 (17)	30 (14)	6 (3)
Pyrexia	14 (11)		14 (18)		2 (17)	1 (8)	30 (14)	1
Insomnia	16 (13)	1 (1)	11 (14)		3 (25)		30 (14)	1
Pharyngitis	15 (12)		14 (18)		1 (8)		30 (14)	
Dizziness	17 (13)		10 (13)		2 (17)		29 (13)	
Dysgeusia	8 (6)		20 (26)				28 (13)	
Urinary tract infection	15 (12)	2 (2)	11 (14)				26 (12)	2
Peripheral edema	14 (11)		10 (13)		1 (8)		25 (12)	
Dehydration	9 (7)	5 (4)	11 (14)	1 (1)	2 (17)		22 (10)	6 (3)
Nail disorder	7 (5)		15 (19)				22 (10)	

Table 1: Treatment-Emergent, All-Causality Adverse Events Summarized by descending frequency occurring in at least 10% of subjects with solid tumours receiving Axitinib monotherapy. Includes Protocols A4061011, A4061012, A4061014, A4061015, A4061022, A4061023, A4061027, A4061035 and A4061044.

Laboratory test results, summarised by maximum grade for subjects with solid tumors who received single-agent Axitinib, are presented in the table below.

Group/Parameter[b]	N	n (%)[a] at Maximum Grade									
		Grade 1		Grade 2		Grade 3		Grade 4		Total	
Chemistry											
Total Bilirubin	347	44	(12.7)	21	(6.1)	2	(0.6)	2	(0.6)	69	(19.9)
Hypoalbuminemia	343	117	(34.1)	39	(11.4)	6	(1.7)	0	(0.0)	162	(47.2)
Aspartate Aminotransferase (SGOT)	347	113	(32.6)	20	(5.8)	11	(3.2)	0	(0.0)	144	(41.5)
Alanine Aminotransferase (SGPT)	345	88	(25.5)	32	(9.3)	7	(2.0)	0	(0.0)	127	(36.8)
Alkaline Phosphatase	339	108	(31.9)	26	(7.7)	6	(1.8)	0	(0.0)	140	(41.3)
Creatinine	347	103	(29.7)	25	(7.2)	0	(0.0)	4	(1.2)	132	(38.0)
Hypernatremia	347	21	(6.1)	1	(0.3)	0	(0.0)	0	(0.0)	22	(6.3)
Hyponatremia	347	108	(31.1)	0	(0.0)	16	(4.6)	0	(0.0)	124	(35.7)
Hyperkalemia	347	74	(21.3)	24	(6.9)	9	(2.6)	0	(0.0)	107	(30.8)
Hypokalemia	347	46	(13.3)	0	(0.0)	4	(1.2)	0	(0.0)	50	(14.4)
Bicarbonate	261	67	(25.7)	9	(3.4)	1	(0.4)	1	(0.4)	78	(29.9)
Hypercalcemia	171	23	(13.5)	1	(0.6)	1	(0.6)	1	(0.6)	26	(15.2)
Hypocalcemia	171	29	(17.0)	11	(6.4)	1	(0.6)	2	(1.2)	43	(25.1)
Hyperglycemia	344	158	(45.9)	56	(16.3)	13	(3.8)	0	(0.0)	227	(66.0)
Hypoglycemia	344	47	(13.7)	10	(2.9)	2	(0.6)	1	(0.3)	60	(17.4)
Hematology											
Hemoglobin	347	134	(38.6)	30	(8.6)	0	(0.0)	3	(0.9)	167	(48.1)
Platelets	346	68	(19.7)	4	(1.2)	1	(0.3)	2	(0.6)	75	(21.7)
White Blood Cells	347	52	(15.0)	12	(3.5)	0	(0.0)	1	(0.3)	65	(18.7)
Neutrophils (Abs)	344	32	(9.3)	10	(2.9)	3	(0.9)	12	(3.5)	57	(16.6)
Lymphocytes (Abs)	345	65	(18.8)	60	(17.4)	29	(8.4)	13	(3.8)	167	(48.4)
Urinalysis											
Urine Protein	337	63	(18.7)	72	(21.4)	11	(3.3)	0	(0.0)	146	(43.3)

Table 2: Laboratory Test Results Reported for Subjects with Solid Tumors Receiving Single-Agent Axitinib Protocols A4061011,A4061012, A4061014, A4061015, A4061022, A4061023, A4061027, A4061035, and A4061044

The ongoing Phase 2 programme includes studies in renal cell carcinoma, breast cancer, non-small cell lung cancer (NSCLC), pancreatic cancer, melanoma, and thyroid cancer. In all of the studies, a starting dose of 5 mg bd was used. Except for the breast cancer study, Axitinib dose titrations in increments of 1-3 mg to the maximum dose of 10 mg bd were allowed in those patients tolerating Axitinib and without treatment with anti-hypertensive medications. All studies allowed dose reductions for drug-related adverse events.

Efficacy has been observed in several solid tumor studies. In the Phase 1 trial (AG013736-001), there were 3 confirmed partial responses among the 36 patients enrolled (2 in renal cell carcinoma, 1 in adenoid cystic carcinoma). In an ongoing Phase 2 cytokine-refractory renal cell carcinoma trial, 24 of 52 subjects receiving single-agent AG-013736 experienced a confirmed partial response (46% response rate). The median TTP was >12 months.

In the Phase 1 portion of a Phase 1/2 study in breast cancer, subjects with metastatic disease received first-line treatment with Axitinib in combination with docetaxel (80 mg/m^2 every 3 weeks). According to investigator report, 2 of the 6 subjects enrolled in Phase 1 portion of the study achieved a confirmed partial response by RECIST. It is too early to report efficacy information from the blinded Phase 2 portion of the study. No objective

responses were observed among 12 subjects enrolled in a Phase 2 trial in poor prognosis AML/MDS. In an ongoing Phase 2 trial testing single-agent Axitinib in thyroid cancer patients, 12 out of 60 patients (20%) have achieved a partial response (PR) by investigator report. The duration of response ranged from 28-333 days. In two ongoing Phase 2 trials testing single-agent Axitinib in metastatic melanoma and NSCLC, partial responses have been reported in both trials.

The effect of hepatic impairment on single-dose Axitinib plasma pharmacokinetics was evaluated in a study (A4061036) that included subjects with mild hepatic impairment (Child-Pugh Class A; n=8), moderate hepatic impairment (Child-Pugh Class B; n=8), and healthy volunteers with normal hepatic function (n=8).

Mild hepatic impairment did not alter Axitinib plasma exposures (AUC0-∞ and Cmax) compared to normal hepatic function. However, there was a ~2-fold increase in axitinib $AUC_{0-\infty}$ and a 1.3-fold increase in Axitinib C_{max} in subjects with moderate hepatic impairment compared to subjects with normal hepatic function (see below).

Treatment Group	C_{max} (ng/mL)		$AUC_{0-\infty}$ (ng.hr/ml)	
	Mean[a]	Ratio[b] (90% CI)	Mean[a]	Ratio[b] (90% CI)
Normal Hepatic Function; n=8	30.4	----	156	----
Mild Hepatic Impairment; n=8	27.0	0.89 (0.49-1.60)	122	0.78 (0.40-1.54)
Moderate Hepatic Impairment; n=8	38.9	1.28 (0.71-2.30)	304	1.95 (1.00-3.83)

Table 3: Hepatic Impairment Study A4061035: Summary of Statistical Analysis of Axitinib Plasma Pharmacokinetics ($AUC_{0-\infty}$ and C_{max}).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives of The AXMUS-C Phase II Randomised Controlled Pilot study in colorectal cancer

Overall aims: Axitinib has been used in the Phase II and III setting in many cancers, with an adequate safety profile. Its role in the treatment of colorectal cancer as monotherapy has yet to be defined.

- To evaluate the efficacy of Axitinib (a VEGF inhibitor) monotherapy in third-line metastatic colorectal cancer and improve clinical outcomes in chemotherapy- refractory metastatic CRC

- To test the potential for dynamic contrast-enhanced ultrasound as a potential novel imaging biomarker of early response against RECIST criteria

Primary objective of trial

- To demonstrate a progression-free survival to Axitinib monotherapy in refractory (to all known conventional treatments) metastatic colorectal cancer

Secondary objectives of trial

- To assess the correlation in patients with a confirmed vascular response (as evaluated by a greater than 20% reduction in CEPHI at 2 weeks).
    - This assessment will be done by separating out the RECIST-progressors (non-responders) who can also be detected by CEPHI at 2 weeks, and comparing this with RECIST responders (CR+PR+SD). The patients receiving Placebo will be included in this analysis.
    - To demonstrate the value of CEPHI as an early imaging selection biomarker of non-response (or response) in patients who have had at least 4 weeks of study treatment.

- To compare overall survival between the treatment and placebo arms
- To compare the overall RECIST response rate between the treatment and placebo arms
- To compare and correlate the 2 week CEHPI and 8 week RECIST response rates.
- To compare the median overall survival of patients receiving Axitinib who develop new diastolic hypertension (>90mmHg) with those that do not (in either/or the blinded placebo group or treatment group combined)
- To identify if CEHPI will function as a non-invasive correlative biomarker of Axitinib pharmacokinetics (PK) and help minimise toxicity and identify responders

- Toxicity (CTC) i for the treatment and placebo arms

2.2 ENDPOINTS

Co-Primary Endpoints

- To assess whether the median progression-free survival is longer in third-line patients with chemo-refractory metastatic colorectal cancer receiving Axitinib monotherapy Versus placebo
- To assess whether the median progression-free survival is shorter in those patients who do not undergo vascular shutdown (defined as ≤ 20% reduction in CEHPI at 2 weeks) compared with those that do undergo vascular shutdown (>20% reduction in CEHPI at 2 weeks).

Secondary Endpoints

- To compare overall survival between the treatment and placebo arms
- To compare duration on study treatment between the treatment and placebo arms
- To compare the best overall RECIST response rate between the treatment and placebo arms
- To compare and correlate the 2-week CEHPI perfusion index and 8 week RECIST response rates in the ITT population
- To compare the median overall survival of patients receiving Axitinib who develop new diastolic hypertension (>90mmHg) with those that do not (in either/or the blinded placebo group or treatment group combined)
- To identify if CEHPI will function as a correlative biomarker of Axitinib pharmacokinetics (PK) and help minimise toxicity and identify responders
- To compare toxicity (CTC) information for the treatment and placebo arms.
    - Type, incidence, severity, timing, seriousness of adverse events by Chemotherapy toxicity criteria (CTC) v4.03 grading.
- Axitinib PK analysis correlation with patients developing or not developing diastolic hypertension

3. Study Design

A Phase II, double-blind, 2 arm pilot randomised placebo controlled trial. 50 patients will be sequentially randomised 2:1 to Axitinib or placebo.

Inclusion criteria: Chemorefractory third-line metastatic CRC with US-assessable liver or other abdominal metastases that can have a baseline DCEUS baseline measurement.

Treatment arm: Axitinib monotherapy started in all patients at 5mg bd, and increased fortnightly by a dose level (See Table 4) as tolerated to a maximum dose of 10mg bd.

Control arm: Placebo (blinded) randomised 2:1 to Axitinib : placebo

Follow up: Outpatient monitoring at 2 weeks and 4 weeks post first dose then 4 weekly thereafter with RECIST restaging every 8 weeks. CEHPI at baseline, 2 weeks and 8 weeks for assessment of differential blood supply (CEHPI) with an optional visit at 48-72 hours post first dose. VEGF-PK samples at Day 15 & Day 28 and at 8 weeks and RECIST progression. At 8 weeks, after tumour CT RECIST assessments, conventional responders (CR/PR/SD) continue monotherapy. In non-responders (PD), monotherapy can be continued if patient chooses to continue and if tolerated. CT response assessments continue at 8 weekly intervals in all patients, with parallel 8 weekly DCE-US. CEHPI at baseline, optionally at 47-72 hours, 2 weeks, 8 weeks and at progression of disease.

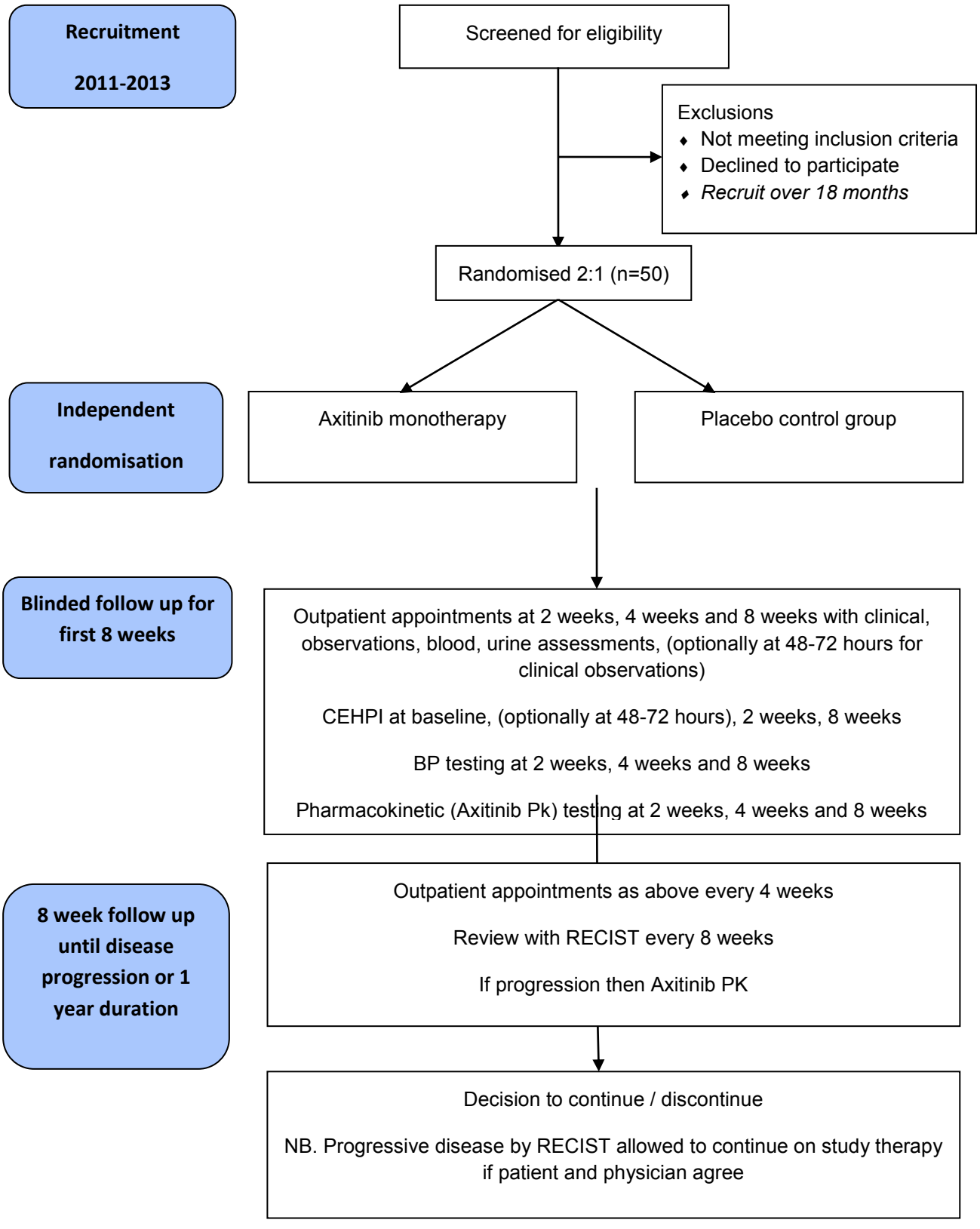
Trial Treatment

Axitinib or placebo will be administered, twice daily (bd) on a continuous daily dosing schedule, to patients randomised to Arm A or Arm B, respectively**.** The starting dose will be 5mg BD which will be increased fortnightly by a dose level (See Table 4) as tolerated to a maximum dose of 10mg bd. Doses should be taken with food as close to 12 hours apart as possible and at approximately the same times each day on a continuous schedule. Patients who tolerate Axitinib/placebo with no adverse events related to Axitinib/placebo above CTCAE Grade 2 for a consecutive 2-week period should have their dose increased by one dose level unless BP is >150/90 mm Hg. [The clinical judgment of the treating physician should be exercised when titrating Axitinib/placebo dose. In cases where it is not obvious whether Axitinib is a contributor to adverse event(s), dose titration will remain at the investigator's discretion.

The study treatment may be permanently discontinued upon progression of disease, occurrence of unacceptable toxicity, withdrawal of patient consent, or other withdrawal criterion is met. However, patients who have progressive disease (PD) but have experienced clinical benefit from Axitinib or placebo treatment will be eligible for continued treatment

provided that the treating physician has assessed the risk/benefit of taking such an approach and no alternative treatment is available.

Patients who require different systemic cancer treatment from what they were assigned at randomization must be withdrawn from the study and followed as described below. After discontinuation of study treatment and the mandated 28-day follow-up period, patients will continue to be followed in order to collect information on further anti-tumour therapy and survival.



4. Subject Selection

4.1. Inclusion criteria

Patients must meet all of the following inclusion criteria for enrolment:

1. Histologically or cytologically confirmed adenocarcinoma of the colon or rectum with liver metastas(es) or other measurable lesion. At least one of which should not have had any focal therapy including radiofrequency ablation.
2. Evidence of uni-dimensionally measurable disease as defined by the Response Evaluation Criteria in Solid Tumours (RECIST).
3. 18 years of age or older.
4. ECOG performance status of 0 or 1.
5. Failed (or intolerant of) at least 2 chemotherapy regimens in advanced disease and resolution of any acute toxic effects of prior therapy e.g. radiotherapy or surgical procedure to NCI CTCv4 grade ≤1. No other alternative available effective treatment options.
6. Adequate organ function as defined by the following criteria:
7. Serum aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine aminotransferase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤5 x upper limit of normal (ULN).
8. Total serum bilirubin <1.5 x ULN
9. Serum albumin ≥25mg/dl
10. Absolute neutrophil count ≥1500/µL
11. Platelets ≥75,000/µL
12. Haemoglobin ≥9.0 g/dL
13. Serum creatinine ≤1.5 x ULN
14. Signed and dated informed consent form
15. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures

4.2 Exclusion criteria

The presence of any of the following will exclude a patient from enrolment:

1. Previously *not* exposed to oxaliplatin **and** irinotecan **and** Flouropyrimidine (5FU or capecitabine) based cytotoxic chemotherapy (prior pelvic radiation therapy including adjuvant or neoadjuvant chemo-radiation therapy for resected rectal cancer is allowed provided it is completed within 4 weeks prior to study entry)
2. Less than 6 months from completion of adjuvant chemotherapy to diagnosis or documentation of recurrent cancer

3. Palliative radiotherapy to non-target, metastatic lesions will be allowed provided it was completed within 4 weeks prior to study entry.
4. Prior surgery within 4 weeks prior to study entry
5. Current treatment within another therapeutic clinical trial.
6. Presence of grade ≥2 peripheral neuropathy.
7. Grade ≥2 thrombocytopenia (i.e., platelet count <75,000/µL), grade 3 neutropenia (i.e., absolute neutrophil count <1500/µL), or grade 3 non-hematologic adverse event associated with prior adjuvant oxaliplatin, irinotecan and/or 5-FU treatment.
8. History of significant bleeding within the past 3 months, including gross haemoptysis or haematuria, or underlying coagulopathy.
9. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 3 months prior to study enrolment, unless affected area has been removed surgically.
10. On-going cardiac dysrhythmias of grade ≥2, atrial fibrillation of any grade, or QTc interval to >450 msec for males and >470 msec for females.
11. Hypertension uncontrolled by medication (>150/100 mmHg despite optimal medical therapy).
12. On-going treatment with therapeutic doses of warfarin (however, low dose warfarin up to 2mg daily for deep vein thrombosis prophylaxis is allowed). Low molecular weight heparin (LMWH) is allowed.
13. Diagnosis of any second malignancy within the last 3 years that is potentially liable to interfere with study outcomes (basal cell carcinoma, squamous cell skin cancer, or in situ carcinoma and hormone controlled locally advanced prostate cancer that has been adequately treated with no evidence of recurrent disease for 12 months, are allowed)
14. History of or known brain metastases, spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease on screening CT or MRI scan.
15. Known human immunodeficiency virus (HIV) infection.
16. Pregnancy, breastfeeding, or unwillingness/inability to employ an effective method of birth control/contraception to prevent pregnancy during treatment and for up to 3 months after discontinuing study drug if of reproductive potential.
17. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that would impart, in the judgement of the investigator, excess risk associated with study participation or study drug administration, or which, in the judgment of the investigator would make the patient inappropriate for entry into the trial.
18. Gastrointestinal abnormalities including: inability to take oral medication; requirement for intravenous alimentation; prior surgical procedures affecting absorption; treatment for active peptic ulcer disease in the past 6 months; active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis or melaena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
19. Current use or anticipated need for treatment with drugs that are known CYP3A4 or CYP1A2 inducers (i.e. carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampin, and St. John's wort).

20. Current use or anticipated need for treatment with drugs that are known CYP3A4 inhibitors (i.e. grapefruit juice, ketoconazole, nefazodone, itraconazole, miconazole, erythromycin, clarithromycin, telithromycin, verapamil, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir and delavirdine)
21. Any of the following within 6 months prior to study drug administration: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack and 6 months for deep vein thrombosis or pulmonary embolism.

4.3. Life Style Guidelines

During the study female patients of childbearing potential must take precautions to prevent pregnancy since the effects 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 these drugs on sperm are unknown. These restrictions should remain in force for 6 months from the last dose of investigational agent. 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 start and should be in agreement with local laws.

5. Study Procedures

5.1. Allocation to Treatment

Participants will be identified from Oncology clinics at Imperial College Healthcare NHS Trust by a member of the clinical research team who has been certified in Good Clinical Practice. Patients will receive detailed information sheets (see appendix) and offered a link to the study website where they can review the study and gain further information.

5.2 Randomisation

Patients will be randomised in a ratio of 2:1 to Axitinib monotherapy or placebo. This will be performed centrally by an independent system (Imperial 'Inform' system 2011) to maintain blinding. Anonymised randomisation details will be kept off site and not disclosed to the study team until follow up is completed.

5.3 Blinding

Patients, sonographers and clinicians will be blinded to therapy. Pharmacy will have an anonymised coding ticket system for dispensing drug/ placebo once randomisation is complete. Unblinding will only occur at the discretion of the data monitoring committee or the investigators in an emergency situation (including out-of-hours), primarily for safety reasons throughout the duration of the trial.

5.4 Drug Supplies (Axitinib and Placebo)

Axitinib and placebo will be supplied for the study by the Global Supply Chain, Pfizer Global Research and Development. Clinical Trial Material (CTM) will be shipped to the study sites with instructions on how to confirm drug receipt.

5.5 Formulation and Packaging

Axitinib and placebo will be supplied as 1 mg and 5 mg film-coated tablets for oral administration in light-protecting bottles.

5.6 Preparation and Dispensing

Axitinib and placebo tablets will be dispensed in opaque plastic bottles to protect from light. Axitinib is a hazardous drug (due to possible reproductive toxicity), and should be handled according to the recommended procedures described in the current edition of the American Society of Hospital Pharmacists (ASHP), Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs, American Hospital Formulary Service (AHFS) Drug Information (1999) and its references. Procedures described in each institution's pharmacy or hospital standard operating procedure manual should be followed when handling hazardous drugs.

5.7 Administration

Study treatment must begin within 7 days of randomization

5.8 Dosing

The recommended starting dose of Axitinib is 5 mg bd taken orally with food. Dose adjustments, including dose increase or dose reduction should be based on adverse events experienced by the individual patient. Axitinib should be taken beginning on Day 1 of the study. Doses should be taken approximately 12 hours apart continuous dosing.

Patients will be instructed to take their doses at approximately the same times each day. Patients will be instructed that if they vomit after taking a dose, that they must not take an extra dose, but instead resume subsequent doses as prescribed. Any missed dose may be taken late up to 3 hours before the next scheduled dose, otherwise, it should be skipped. If doses are missed or vomited, this must be indicated in the source documents and CRFs. Study treatment will be administered in cycles of 4 weeks in duration.

Patients who tolerate Axitinib with no adverse events related to study drug above CTCAE Grade 2 for consecutive 2-week period should have their dose increased by one dose level (see Table 4) to a maximum of 10 mg bd (unless the patient's blood pressure is >150/90 mm Hg or the patient is receiving antihypertensive medication). Patients experiencing drug reaction greater than CTCAE Grade 2 should undergo dose modification. For the patients receiving Axitinib, concomitant medications that are known to substantially inhibit the enzyme, CYP3A4, should be avoided as much as medically possible. The clinical judgment, taking into account all of these parameters, of the treating physician should be exercised in titrating Axitinib dose.

Available Axitinib Dose Levels	**Dose**
+2	10 mg BD
+1	7 mg BD
0 (Starting Dose)	**5 mg BD**
-1	3 mg BD
-2	2 mg BD

Table 4: Axitinib dose modification table

5.9 Dose Interruption and Reduction

Adverse events and other symptoms will be graded according to the current Common Terminology for Adverse Events version 4.03.

5.10 Management of Axitinib-Related Adverse Events

This section contains management of adverse events except hypertension and proteinuria which are discussed in subsequent sections. Patients developing Axitinib related CTCAE Grade 1 or 2 adverse events may have their dose continued at the same dose level (See Table 4). Patients removed from treatment for intolerable toxicity should still be followed with regular tumour assessments until disease progression or start of new treatment, and for survival thereafter.

Related Adverse Events	INTERVENTION
Grade 1	Continue at same dose level
Grade 2	Continue at same dose level
Grade 3 non-haematologic treatment-related toxicity*	Decrease dose to one lower dose level
Grade 4 non-hematologic treatment-related toxicity or Grade 4 hematologic toxicity**	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 BD, contact sponsor for discussion prior to implementation.

Table 5: Adverse event action plan

* Patients who develop Grade 3 non-haematologic toxicities that are controlled with symptomatic medications or Grade 3 asymptomatic biochemistry laboratory abnormalities may be continued at the same dose level at the discretion of the investigator.

** Patients who develop Grade 4 lymphopenia or Grade 4 asymptomatic biochemistry laboratory abnormality may continue study treatment without interruption.

5.11 Axitinib/Placebo Dose Reduction for Hypertension

Patients treated with Axitinib/placebo will be issued blood pressure cuffs (provided by Pfizer Inc) for home monitoring and instructed to measure their blood pressure (BP) twice daily, prior to taking each dose. All blood pressure measurements will be recorded in a diary and brought to the nurse or study coordinator at each clinic visit. Patients should be instructed by the study staff to contact their physician for guidance if their systolic blood pressure rises above 140 mm Hg, diastolic blood pressure rises above 90 mm Hg, or if they develop symptoms perceived to be related to elevated BP (eg, headache, visual disturbance). See below for dose modifications for hypertension. A different blood pressure threshold for contacting physician may be used according to the physician's clinical judgment. See below for dose modifications for hypertension.

New or additional antihypertensive therapy (see Section 5.4, Concomitant Medication(s) for guidance) should be started if 2 BP readings, preferably taken in the clinic and separated by at least 1 hour, show the following: 2 systolic BP readings greater than 140 or 2 dBP readings greater than 90 mm Hg. Alternately, the dose of existing antihypertensive medication(s) may be increased. Investigator may use clinical judgment to start new or additional antihypertensive therapy at a lower blood pressure threshold. If the patient is already on maximal antihypertensive treatment, the Axitinib dose should be reduced by 1 dose level (see Table 4).

Patients who have 2 systolic BP readings, separated by at least 1 hour, greater than 160 mm Hg, or 2 dBP readings, separated by at least 1 hour, greater than 105 mm Hg, will have treatment with Axitinib/placebo held. (Note: if Axitinib/placebo is held, patients receiving antihypertensive medications should monitor closely for hypotension and restart Axitinib/placebo at one lower dose level (see Table 4) as soon as BP is <140/90 mm Hg. The plasma half-life of Axitinib is 2 – 4 hours and BP usually decreases within 1-2 days following dose interruption.)

Patients removed from treatment for intolerable toxicity should still be followed with regular tumour assessments until disease progression or start of new treatment, and for survival thereafter.

Degree of Blood Pressure Elevation			
Systolic Pressure	OR	Diastolic Pressure	Management
2 BP readings separated by at least 1 hour show systolic pressure >150 mm Hg		2 BP readings separated by at least 1 hour show diastolic pressure >100 mm Hg	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 BP readings separated by at least 1 hour show systolic pressure >160 mm Hg	OR	2 BP readings separated by at least 1 hour show diastolic pressure >105 mm Hg	Stop Axitinib; adjust antihypertensive medication; as soon as BP is less than 150/100 mm Hg, restart Axitinib at one lower dose level.
Recurrent hypertension following previous dose reduction (2 BP readings separated by at least 1 hour show systolic pressure >150 mm Hg)	OR	Recurrent dBP >100 mm Hg (2 BP readings separated by at least 1 hour) following previous dose reduction	Repeat Axitinib dose reduction by one lower dose level. If a patient requires dose reduction below 2 mg BD, contact Sponsor for discussion

Table 6: Hypertension management plan

5.12 Axitinib/Placebo Dose Reduction for Proteinuria

- If dipstick shows > 2+ proteinuria, perform 24 hour urine collection. Dosing may continue while waiting for test results.

- If < 3.5 g proteinuria/24 hour is reported, continue dosing at the same dose level.

- If > 3.5 g proteinuria/24 hours is reported, hold dosing and repeat 24 hour urine collection for proteinuria and creatinine clearance (interval at investigator discretion)
  until proteinuria is < 3.5 g/24 hours. Restart Axitinib/placebo at the same dose or one lower dose level at the discretion of the investigator.

Patients removed from treatment for intolerable toxicity should still be followed with regular tumour assessments until disease progression or start of new treatment, and for survival thereafter.

5.13 Axitinib/Placebo Dose Interruption for Surgery or Surgical Procedures

If a major surgery or an interventional procedure (eg, endoscopy) is required, treatment with Axitinib/placebo must be interrupted at least 24 hours before the procedure and the patient blood pressure should be monitored closely for hypotension. Patients may receive further study treatment 2 weeks after surgery or 1 week after interventional procedure based on the judgment of the treating physician and principal investigator, if the reason for procedure is other than disease progression.

5.14 Compliance

Patients will maintain diaries to include missed or changed doses. Pill counts on returned study drug bottles should be performed.

5.15 Drug Storage and Drug Accountability

Axitinib/placebo will be supplied for the study by the Pharmacy Operations Office, Pfizer. CTM will be shipped to the study sites with an Investigational Drug Receipt Confirmation form. This form should be completed with protocol number, drug name, lot number, quantity received and condition upon receipt. A copy of the form must be returned via fax to the Pharmacy Operations Office within 24 hours of receipt. A copy will also be returned via mail. The investigator, or an approved representative (eg, pharmacist), will ensure that all Axitinib/placebo is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Drug should be stored at controlled room temperature (ie, 15-30°C), and protected from light and moisture. To ensure adequate records, all Axitinib/placebo will be accounted for in the case report form and drug accountability inventory forms as instructed by Pfizer. Unless otherwise authorized by Pfizer, at the end of the clinical trial all drug supplies unallocated or unused by the subjects must be returned to Pfizer.

Axitinib/placebo is considered a hazardous drug (due to possible reproductive toxicity), and should be handled according to the recommended procedures described in the current edition of the ASHP, Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs, AHFS Drug Information (1999) and its references. Procedures described in each

institution's pharmacy or hospital standard operating procedure manual should be followed when handling hazardous drugs.

5.16 Concomitant Medication(s)

No other chemotherapy or experimental anticancer medications will be permitted while the patient is on study. Any disease progression requiring other forms of systemic anticancer therapy will be cause for discontinuation from study treatment. Palliative radiotherapy is allowed for pain control ONLY to sites of bone disease present at baseline.

5.17 Axitinib/Placebo

Palliative and supportive care for disease-related symptoms, including pain medications, will be allowed to all patients on this trial. 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 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 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/placebo 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.

In vitro studies with human liver microenzymes and recombinant CYP enzymes indicated that Axitinib metabolism was primarily mediated by the drug-metabolizing enzyme CYP3A4/5, and to a lesser extent by CYP1A2, CYP2C19 and uridine glucuronosyltransferase (UGT) 1A1. Clinically, there is likelihood that Axitinib plasma concentrations may be increased in the presence of co-administered potent inhibitors of the CYP3A4/5 enzymes. In a healthy volunteer study, ketoconazole, a potent CYP3A4/5 inhibitor, produced a 2-fold increase in plasma exposure and a 1.5-fold increase in peak plasma concentration of Axitinib. Therefore a potential exists for drug-drug interactions with potent CYP3A/5 inhibitors such as grapefruit juice, ketoconazole, nefazodone, itraconazole, miconazole, erythromycin, clarithromycin, telithromycin, verapamil, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir and delavirdine. Patients who require concomitant treatment with CYP3A/5 inhibitors are not eligible for this study.

Axitinib metabolism may be induced in patients taking potent CYP3A4/5 or CYP1A2 inducers (carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, amobarbital, phenytoin, primidone, rifabutin, rifampin, nevirapine, and St John's wort) and this may reduce Axitinib plasma concentrations. Patients who require concomitant treatment with potent CYP3A4/5 or CYP1A2 inducers are not eligible for the study. Since CYP1A2 is also known to be induced in chronic smokers, there is likelihood that Axitinib plasma concentrations may be reduced in these individuals. (Note: these patients are not excluded from enrolment, however.)

The ability of Axitinib to increase concentrations of co-administered drugs was also investigated in studies with human liver microsomes. At expected therapeutic plasma concentrations (0.01 to 1.0 µg/mL), Axitinib appears most likely to inhibit the drug metabolizing enzymes CYP1A2 and CYP2C8, 2 enzymes not frequently observed as predominant drug metabolizing enzymes. Theophylline and tacrine are among the few drugs whose plasma concentrations are likely to be increased by Axitinib.

Axitinib is highly bound to proteins in human plasma (99.0% bound at concentrations between 0.2-20 µg/mL). Therefore, drug interactions with other agents that are also highly bound to plasma proteins are a possibility.

Patients who need to be on chronic antacid therapy with histamine H2 antagonists (e.g., cimetidine [Tagamet®], famotidine [Pepcid®], nizatidine [Axid®], ranitidine [Zantac®]), proton-pump inhibitors (eg, lansoprazole [Prevacid®], rabeprazole [Aciphex®], pantoprazole [Protonix®], and esomeprazole [Nexium®]), or locally acting antacids (eg, Maalox®, Milk of Magnesia®, Amphojel®) should stagger the timing of their Axitinib and antacid dosing. Patients should avoid use of antacids for 2 hours before through 2 hours after taking Axitinib/placebo tablets. Note, however, that patients taking the proton-pump inhibitor omeprazole (Prilosec®) are not eligible for this study and that patients should not use omeprazole while taking Axitinib/placebo tablets because omeprazole is a CYP1A2 inducer.

Axitinib is not likely to have drug-drug interactions with commonly used antihypertensive agents belonging to the class of ACE inhibitors including angiotensin II receptor antagonists (e.g., enalapril, captopril, losartan, valsartan), beta-blockers (e.g., atenolol, metoprolol, labetalol), or diuretics (e.g., hydrochlorothiazide, furosemide). Within the class of calcium channel blockers, verapamil, and to a lesser extent nifedipine, nicardipine, and diltiazem have a potential for increasing plasma Axitinib plasma concentrations, due to CYP3A4/5 inhibition and should not be used as first choice in antihypertensive treatment. Other calcium channel blockers (e.g., amlodipine, bepridil, felodipine) are less likely to raise Axitinib plasma levels.

The above information is based on preclinical data from studies using human and animal metabolising enzyme systems.

All concomitant medications and blood products, as well as interventions (e.g., analgesic use or paracentesis) received by patients from the first dose of Axitinib until the end of study visit will be recorded on the CRF.

5.18 Salvage Therapy

Patients who discontinue treatment on this study may receive other experimental treatments or be offered studies if felt to be appropriate.

6. Study Procedures

6.1 Screening

Demographic data, clinical history, response to previous treatments, functional status, imaging and histology results to date will be ascertained at baseline on a standard case report form (CRF). Patients will be eligible irrespective of k-ras mutation status.

The following screening procedures will be performed within up to 28 days prior to the start of treatment on study, unless otherwise stated:

- Patient signature on informed consent form (up to 28 days prior to treatment)
- Medical history including confirmation of histological diagnosis, history of other concomitant illnesses
- Demographics (including age, sex, and race)
- Physical examination including examination of major body systems, ECOG performance status, body weight, height (screening only), and vital signs (temperature, blood pressure, heart rate)
- Haematology performed within 7 days from treatment start
- Chemistry, CEA and CA19.9 performed within 7 days from treatment start
- Coagulation (APTT & INR) performed within 7 days from treatment start
- Thyroid Function Tests (free T3, free T4 and TSH)
- Pregnancy test (urine), if applicable, performed within 7 days from treatment
- Urinalysis by dipstick
- 12-Lead electrocardiogram
- Endoscopy or upper GI imaging, to exclude patients with suspected oesophageal varices and/or gastroduodenal ulcer.
- Assessment of concomitant medications and treatments
- Assessment of ongoing symptoms/events (serious adverse events must be recorded from time of signed consent)
- Study randomisation upon completion of all screening assessments
- Baseline (screening) tumour assessments require CT/MRI (no chest x-ray) of the chest and abdomen at the minimum. If the interval between any of the baseline tumour assessments and randomisation is >28 days, the baseline tumour imaging will be repeated.

6.2 Study Period

Patients will receive dosing of study drug (Axitinib or placebo) as outpatients from the baseline visit. Patients will be followed up at 48-72 hours (optional), 2, 4 and 8 weeks, then monthly thereafter to a maximum of 1 year after the last patient is randomised. Clinic visits

will be performed, and haematology, clinical chemistry, urinalysis, thyroid function tests, and other safety laboratory tests, will be done as shown in the Schedule of Activities. No other chemotherapy agents will be employed during this time, however medicine to provide relief of symptoms will be allowed. Patients will undergo 8 weekly response monitoring with CT imaging as per standard RECIST evaluation v.1.1.

If significant toxicity (CTCAE Grade ≥3) is encountered, subsequent assessments may be performed as necessary to evaluate the specific toxicity until it resolves to baseline or CTCAE Grade ≤1. Additional clinic visits may be required at the discretion of the investigator.

6.3 End of Treatment

The study treatment may be permanently discontinued upon progression of disease, occurrence of unacceptable toxicity, withdrawal of consent, or another withdrawal criterion, unless there is sufficient evidence of clinical benefit to justify continuation of study treatment at the discretion of the investigator. However, patients who require different cancer treatment from that assigned at randomisation must be withdrawn from the study and followed as described below.

After discontinuation of study treatment and the mandated 28-day follow-up period, patients will be followed in order to collect information on further anti-tumour therapy and survival. Patients discontinuing study treatment without documented evidence of disease progression should continue tumour imaging assessments at the same frequency until disease progression, or initiation of another anticancer treatment, whichever is earlier.

The primary reason for a patient's discontinuation of the test drug will be clearly documented on the CRF. Assessments should be performed as outlined in the patient schedule above. At the end of the study or at withdrawal, the following procedures should be performed if they were not performed during the last week:

- Physical examination of major body systems, ECOG performance status, body weight, and vital signs
- Haematology, blood chemistry, coagulation tests, and urinalysis
- CT or MRI scans of chest and abdomen in addition to any other applicable sites of disease
- Assessment of adverse events. Adverse events that are serious, suspected to be related to study drug, or considered significant by the investigator must be followed after the time of therapy discontinuation until the event or its sequelae resolve or stabilise at a level acceptable to the investigator or his/her designated representative. Each serious adverse event (SAE) must be reported to the Imperial College, Pfizer, MHRA and REC
- Assessment of concomitant medications and treatments
- Assessment of Axitinib/placebo compliance/accountability

6.4 Subject withdrawal

When patients are permanently withdrawn from treatment, the primary reason for discontinuation must be provided. Reasons for discontinuation include:

- Death;
- unacceptable toxicity
- RECIST defined disease progression; however, patients who have progressive disease but have experienced clinical benefit from the treatment will be eligible for continued treatment provided that the treating physician has assessed the risk/benefit of taking such an approach and no alternative treatment is available.
- protocol deviation (post study start, includes subject noncompliance);
- pregnancy
- patient choice
- withdrawal of patient consent (cessation of follow-up)
- study terminated by Pfizer, Imperial College or independent safety committee

The reason for a patient's discontinuation from treatment will be documented in the end of study/withdrawal CRF. Patients will be followed for at least 28 days after the last dose of study drug for adverse events. Patients who discontinue the study prematurely will not be replaced. All efforts should be made to continue to follow a patient for survival if he/she withdrew from study treatment for reasons other than death.

Subjects may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioural, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

If the subject withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.5 Follow Up Visits

Patients should continue to be evaluated for 28 calendar days after the last dose of study drug (Axitinib or placebo). During the post-treatment follow-up visit, the following procedures should be performed:

- Physical examination, weight, vital signs, and ECOG
- Assessment of adverse events
- Assessment of concomitant medications and treatments

In the event a patient is unable to return to the clinic for the follow-up visit, telephone contact with the patient to assess adverse events and concomitant medications and treatments is expected. If laboratory assessments are needed to follow-up unresolved adverse events, retrieval of assessments performed at an institution local to the patient is acceptable.

The outcome of adverse events with a date of onset during the study period should be re-evaluated, and any new adverse events should be recorded. All serious adverse events, and those non-serious adverse events assessed by the investigator as possibly related to study drug should continue to be followed even after patient withdrawal from study. These adverse events should be followed until they resolve or until the investigator assesses them to be “chronic” or “stable.”

6.5.1. Additional Follow Up Visits

If patient discontinues the study drug for reasons other than PD, subsequent visits may be every 8 weeks, which will include tumour assessments, until PD or a subsequent anti-cancer therapy is initiated. The following assessments should be completed:

- Tumour assessments according to the study schedule until PD.
- Recording of any new anti-cancer therapy (a tumour assessment is mandatory before initiating the new therapy).

6.6 Survival Follow-up

All patients will be followed for survival every 2 months for at least 1 year after randomisation of last patient. Information regarding systemic therapy, radiation or local therapy, and surgery during survival follow up will also be collected. Premature termination of this clinical trial may occur because of a Imperial College decision, regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of Axitinib at any time.

Regardless of the reason for termination, all data available for the patient at the time of

discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented. In terminating the study, the investigators will ensure that adequate consideration is given to the protection of the patients' interest.

7. Assessments

7.1. Efficacy Assessment

Baseline (screening) tumour assessments require CT/MRI (no chest x-ray) of the chest and abdomen at the minimum. If the interval between any of the baseline tumour assessments and randomisation were to become >28 days, the expired baseline tumour imaging must be repeated. At baseline, tumour lesions will be categorized as target or non-target. All patients will be evaluated for response according to RECIST version 1.1.

CT or MRI of brain at screening and subsequent imaging of brain may be performed if clinically indicated as determined by the treating physician. Bone scan at screening and subsequent imaging of bone may be performed if clinically indicated as determined by the treating physician.

For all patients, CT/MRI (covering the same anatomy as the baseline scans, except brain) will be required every 8 weeks by calendar.

Response (CR/PR) requires confirmation with CT/MRI at least 4 weeks after the response is first noted. These tumour assessments must be performed as scheduled until progression of disease or death regardless of whether patient is receiving study medication or not until permanent withdrawal from study treatment. If a patient is to start a new therapy, these tumour assessments should be repeated prior to start of the new therapy.

The same method and technique should be used to characterize each identified and reported lesion at baseline and during the study treatment period. Imaging-based evaluation over clinical examination is the required technique when both could be used to assess the anti-tumour effect of the treatment. Clinical evaluation of superficial lesions should not be used for tumour measurement. Tumour evaluation by positron emission tomography (PET) scan or by ultrasound may not substitute for CT or MRI scans.

If a patient develops new or worsening pleural effusion or ascites that is large enough for thoracentesis or paracentesis, a fluid sample should be obtained for cytological examination to determine whether the fluid collection is malignant unless there is a reasonable clinical contra-indication to do so. If fluid cytology is negative for malignant cells (defined as non-positive for presence of malignant cells, including “negative”, “atypical” or “indeterminate”), then the new or enlarging fluid collection alone should not be used as evidence of PD. If fluid cytology is positive (including “positive” or “malignant”), then “PD” will be assigned.

All patients’ files must be available for CRF source verification.

7.2. Physical Examination

A complete physical examination including the assessment of all body systems (including neurological assessment), the measurement of body weight, height, heart rate, temperature, and assessment of ECOG performance status (See Appendix 2) will be performed prior to the first dose. A single 12 lead ECG should be performed on all patients at screening. If the mean QTc interval is prolonged (>500 milliseconds), then the ECG should be re-read by a cardiologist or other qualified person at the site for confirmation. Additional ECGs may be performed as clinically indicated. After the initial complete examination, targeted examinations based on signs and symptoms may be performed. All examinations must be performed by qualified health care professionals. Findings of all physical examinations should be recorded in the source documents, and any change from baseline considered by the investigator to be clinically significant should be recorded as an adverse event in the case report form.

7.3 Blood Pressure Assessments

Blood pressure readings should be taken in the seated position after the patient has been sitting quietly for 5 minutes and are required at each clinic visit. All patients receiving study drug will be issued a BP measurement diary. Blood pressure readings should be taken in the seated position after the patient has been sitting quietly for 5 minutes. Patients should be instructed to inform their doctor immediately if their systolic BP rises above 140 mm Hg, dBP rises above 90 mm Hg, or if they develop symptoms perceived to be related to elevated BP (e.g. headache, visual disturbance). A different home blood pressure threshold for contacting physician may be used according to the physician's clinical judgment.

7.4. Urinalysis

The following urinalysis will be performed by routine laboratory test at the intervals described in the Schedule of Tests and Procedures Table: protein, glucose, and blood. Patients with 2+ proteinuria will have protein quantified by 24-hour urine protein determination.

7.5. Haematology

The following haematology tests will be performed at the intervals described in the Schedule of Tests and Procedure Tables: haemoglobin (Hgb), white blood cell count (WBC), WBC differential and platelet count. For patients experiencing erythrocytosis (elevated Hgb), regular phlebotomy should be considered to maintain normal Hgb.

7.6. Biochemistry

The following clinical chemistry tests will be performed at the intervals described in the Schedule of Events: creatinine, sodium (Na+), potassium (K+), chloride (Cl-), calcium (Ca+), alkaline phosphatase, lactate dehydrogenase (LDH), alanine aminotransferase (ALT, or SGPT), aspartate aminotransferase (AST, or SGOT), total protein, albumin, total bilirubin, glucose, phosphate, gamma-glutamil-transpeptidase (GGT), and AFP.

7.7. Thyroid Function Tests

Serum or plasma Thyroid Function Tests (free T3, free T4 and TSH) should be performed for all randomized patients (in both study arms) at baseline (C1D1 or within 7 days of pre-dose). Subsequently TSH should be done at 2 weeks, 4 weeks and 8 weeks after stating therapy and 4 weekly thereafter until 4 weeks after the final dose. Subsequent free T3, free T4 should be performed when clinically indicated. Patients 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.

7.8 Contrast Enhanced Hepatic Perfusion Index

The contrast enhanced hepatic perfusion index will be performed as follows at baseline, 2 weeks and 8 weeks as a putative early response biomarker:

1. Patient is instructed to fast for 4 hours pre-procedure
2. CEHPI performed with patient supine using iu22 ultrasound platform, C5-1 ultrasound probe, general contrast settings (mechanical index 0.06, maximum dynamic range) and 2.4ml of intravenous SonoVue through a 20G or larger cannula or chemotherapy line.
3. Patient then takes medication with food, allowing pharmacokinetic samples to be taken using this as a trough point.

The procedure is outlined in more detail in Appendix 5.

7.9 Axitinib Pharmacokinetic Assessments

No baseline pharmacokinetic testing is required as the value is known to be zero in those who have not received Axitinib.

On day 15 (day of CEHPI) medication will be taken after the ultrasound examination (time zero). After this blood samples will be taken at:

- 1 hour post dose
- 2 hours post dose
- 4 hours post dose

This will be repeated on day 28 and at restaging after 8 weeks at the usual clinic appointments. If there is disease progression pharmacokinetic testing will additionally be performed.

7.9.1. Collection, Processing, Storage and Shipment of Pharmacokinetic Samples

A 3 ml whole blood sample will be collected into K3-EDTA tubes to provide a minimum of 1 ml plasma for pharmacokinetic analysis and will be centrifuged (samples should be kept on ice or at 4°C until centrifugation), protected from light, at 1000 x g (at minimum) for 15 minutes at 4°C to separate the plasma. Plasma will be stored in appropriately labelled plastic amber cryovials at -20°C or lower until analysis. Plasma concentrations of Axitinib from patients on the active Axitinib treatment arm will be analysed using a validated analytical method in compliance with Pfizer standard operating procedures.

The following special precautions should be taken to minimize the rapid degradation of Axitinib in plasma when exposed to visible light:

- Following collection of blood samples, samples should be processed as soon as possible. Preferably, harvested plasma should be frozen within 1 hour of collection.
- Vacutainer tubes should be protected from light (covered completely in aluminium foil or in black protection tubes) while samples are waiting to be centrifuged to harvest plasma.
- Following centrifugation, plasma should be transferred rapidly to labelled plastic amber cryovials and stored at –20°C or lower.
- All samples should be transferred to an opaque box to protect from light exposure during storage and shipment. If a sample is inadvertently exposed to light (for 5 minutes or more), the sponsor should be notified so that the sample can be flagged for possibly spurious results.
- Once frozen, samples should not be allowed to thaw, including during shipment.
- Samples will be shipped with the completed sample inventory form and sufficient dry ice to last for at least two days.

8. Adverse Event Reporting

8.1 Adverse Events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (See Section Appendix 4) requiring immediate notification to Imperial College, Pfizer or its designated representative, MHRA and REC. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.2. Reporting Period

Serious adverse events require immediate notification to Imperial College, Pfizer or its designated representative, MHRA and REC beginning from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the clinical trial, ie, prior to undergoing any trial-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

- Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of trial treatment through last subject visit.
- If a subject begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Additionally, they may include the signs or symptoms resulting from:
- Drug overdose;
- Drug withdrawal;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Extravasation;
- Exposure in utero.

Worsening of signs and symptoms of the malignancy under trial should be reported as adverse events in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

Test result is associated with accompanying symptoms, and/or;

- Test result requires additional diagnostic testing or medical/surgical intervention, and/or;
- Test result leads to a change in trial dosing (outside of protocol-stipulated dose
- adjustments) or discontinuation from the trial, significant additional concomitant drug
- treatment, or other therapy, and/or;
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5. Serious Adverse Events

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

Progression of the malignancy under trial (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal during the trial or within the safety reporting period. Hospitalisation due to signs and symptoms of disease progression should not be reported as serious adverse event. If the malignancy has a fatal outcome during the trial or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with CTC Grade 5.

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalisation. However, if it is determined that the event may jeopardize the subject and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in accident & emergency or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse. Adverse events reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

8.6. Hospitalisation

Adverse events reported from clinical trials associated with hospitalisation, or prolongation of hospitalisation, are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). Hospitalisation does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new adverse event or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the trial protocol);
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery);
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.7. Severity Assessment

If required on the adverse event case report forms, the investigator will use the following definitions of severity in accordance with Cancer Therapy Evaluation Program, CTCAE version 4.03 to describe the maximum intensity of the adverse event. If the event is serious, the CTC grade reported in the adverse event CRF must be consistent with the description of CTC grade included in the narrative section of the serious adverse event report.

Grade	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 3.0 document but may be used in certain circumstances.)
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING OR DISABLING Adverse Event
5	DEATH RELATED TO Adverse Event

Classification of severity of adverse events.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on trial records. In addition, if the investigator determines a serious adverse event is associated with trial procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.9. Exposure In Utero

For investigational products within clinical trials and for marketed products, an Exposure In Utero (EIU) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);
- A male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure)

If any trial subject or trial subject's partner becomes or is found to be pregnant while receiving the investigational product, the investigator must submit this information to

Imperial College, Pfizer, MHRA and REC on an EIU Form. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and then notify Imperial College, Pfizer, MHRA and REC of the outcome. The investigator will provide this information as a follow up to the initial EIU Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a serious adverse event case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted foetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting serious adverse events. In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before an EIU Form can be completed). The "normality" of an aborted foetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly. Additional information about pregnancy outcomes that are classified as serious adverse events follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as possibly related to the *in utero* exposure to the investigational medication should be reported.

Additional information regarding the exposure *in utero* may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator must obtain permission from the subject's partner in order to conduct any follow-up or collect any information

8.10. Withdrawal Due to Adverse Events (See also Subject Withdrawal)

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page. When a subject withdraws due to a

serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.11. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial subject. In addition, each trial subject will be questioned about adverse events.

8.12. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.12.1 Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Imperial College, Pfizer, MHRA and REC are to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to Imperial College, Pfizer, MHRA and REC must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of EIU cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient trial subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her

For all serious adverse events, the investigator is obligated to pursue and provide information to Imperial College, Pfizer, MHRA and REC in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Imperial College, Pfizer, MHRA and REC to obtain specific additional follow-up information in an

expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Imperial College, Pfizer, MHRA and REC or its designated representative.

8.12.2. Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events are to be reported on the adverse event CRFs, which are to be submitted to Imperial College, Pfizer, MHRA and REC. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.13. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction related to Axitinib that is both unexpected and serious is to be reported within 24 hours of awareness of the reaction by the investigator. In particular, if the serious adverse reaction is fatal or life-threatening, notification to Imperial College, Pfizer, MHRA and REC must be made immediately, irrespective of the extent of available adverse reaction information. Reporting will be collected on the adverse reaction CRFs, which are to be submitted to Imperial College, Pfizer, MHRA and REC. Adverse reactions should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse reaction information.

9. Statistical Analysis

9.1 Size of treatment effect

This novel project is a Pilot Phase II double-blinded, placebo controlled randomised (2:1 Axitinib : Placebo) for 50 patients. This sample size would not normally allow for conventional or adequate powering of a study based on OS, PFS or RR. This is a pilot study of assessing efficacy of axitinib monotherapy in colorectal cancer. The primary end-point is PFS by conventional RECIST. If a difference of more than 6 weeks improvement in PFS is observed, then a funding application to Pfizer and UK NCRN will be made for an adequately powered phase III study.

As a secondary and exploratory analysis, the major interest is whether we can better select (or predict) the population that benefits from Axitinib within the next generation of study design. If our secondary hypothesis is correct, then in those patients who receive Axitinib, a significant proportion will have ultrasound detectable changes in reduction in blood flow. i.e. a significant pharmacodynamic effect on the tumour vasculature measured via the US biomarker index (CEHPI). In our preliminary work (Gauthier et al, 2011), a 20% change in CEPHI was significant and also allowed for measurement error. Thus, this study will therefore examine the survival difference between CEPHI responders (those whose CEPHI falls by ≥20%) versus non-responders. A clinically meaningful difference in survival in these groups would be a difference of at least 6 weeks. If this end-point is achieved, it would be a positive signal to design an adequately powered phase III powered for OS. This would allow enrichment for patients who potentially benefit, but also allow discontinuation in patients at 2 weeks who will not benefit, saving unnecessary treatment and toxicities. This approach of personalised medicine using biomarkers (in this case CEPHI) is the direction of almost all cancer studies.

The conventional PFS and OS for this cohort of chemo-refractory patients is 6-8 weeks and 4-6 months respectively. This is the first study with Axitinib in this setting. Our aim with 50 patients is to generate data for a sample size calculation for a randomised phase III. In the only comparative Phase 2 study (A6181003) with a similar compound, is of Sunitinib in chemorefractory metastatic colorectal cancer, 84 patients were enrolled and 82 were actually treated with Sunitinib. 10% discontinued due to adverse events. The ITT analyses for PFS was less than 2 months but OS still showed an encouraging overall survival of 10.2 months. Of greater interest, 1 patient with prior Bevacizumab therapy had a partial response; 24 patients (29%) had a best response of stable disease, 13 patients had SD ≥22 weeks. (This demonstrates the reason for doing our analysis as a sub-population has benefited significantly from Axitinib's parent compound and with CEPHI – we hope to predict this group). In our study, we would thus expect around 15-18 of the treated patients to have prolonged progression-free survival of this order of magnitude, and the placebo treated patients will act as a contemporaneous control. If the 2 week CEPHI index is highly predictive of survival in this group, then selection on this basis for a phase III trial will enrich the potentially benefitting population even further.

9.2 Statistical analysis plan

The primary analysis will be on PFS by Kaplan-Meier of patients who manage to complete at least 2 weeks of Axitinib therapy (versus Placebo).

For the secondary analyses:-

A stratified log-rank test (1-sided, p=0.025) will be used to compare PFS between CEHPI responders and non-responders. The median event time and 2-sided 95% CI for the median will be provided. The hazard ratio and its 95% CI will be also estimated.

The optimum CEHPI cut-point for determining response will be confirmed using the percentage change in CEHPI against RECIST response using a receiver operator characteristic curve. Test statistics including sensitivity, specificity, positive predictive value, negative predictive value, odds of disease progression and area under the curve will be calculated for 2 week CEHPI reduction in predicting disease progression.

A similar analysis will be performed with diastolic blood pressure.

Overall survival is defined as the time from date of randomisation to date of death due to any cause. For patients not expiring, their survival times will be censored at the last date they are known to be alive. Patients lacking data beyond the day of randomisation will have their survival times censored at the date of randomisation with duration of 1 day. Overall survival will be summarised using Kaplan-Meier methods and displayed graphically where appropriate. A stratified log-rank test (1-sided, p=0.025) will be used to compare OS between CEHPI responders and non-responders. The median event time and 2-sided 95% CI for the median will be provided. The hazard ratio and its 95% CI will be also estimated.

9.3 Pharmacokinetic (PK) analysis

The PK's of Axitinib will be correlated with the CEPHI index. It is not currently known whether a specific level of PK is required for threshold effect on vasculature shut-down, or whether there is constant linear relationship to dose. This is the first study that may understand this better.

9.4 Safety Analysis

Frequencies of patients experiencing at least one AE will be displayed by System Organ Class and Preferred Term according to MedDRA terminology. Detailed information collected for each AE will include a description of the event, duration, severity, seriousness, study drug relatedness, action taken, and clinical outcome. Severity of the AEs will be graded according to the NCI CTCAE version 4.03. The analysis will be performed on AEs classified as treatment emergent.

Summary tables will present the number of patients observed with AEs and corresponding percentages. The denominator used to calculate incidence percentages consists of patients receiving at least 1 dose of study medication. Within each table, the AEs will be categorized by MedDRA system organ class and preferred term. Additional subcategories will be based on event intensity and relationship to study drug. Individual patient listings will be prepared for all AE data.

9.5 Analysis of clinical laboratory data

Haematology and blood chemistry data will be graded according to NCI CTCAE version 4.03 severity grade. The frequencies of the worst severity grade observed will be displayed for each parameter.

Listing tables will be prepared for each laboratory measure, and will be structured to permit review of the data by patient as they progress on treatment. Summary tables will be prepared to examine the distribution of laboratory measures over time. Shift tables may be provided to examine the distribution of laboratory toxicities.

9.6 Concomitant medications

All medications received during the treatment period will be considered as concomitant medications and will be coded by WHO medical dictionary; patients who received concomitant medications will be listed.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, periodic monitoring performed by the Imperial College Trials Unit will ensure that the protocol and GCPs are being followed. An independent data committee and the Imperial 'INFORM' database will aid in this process. The committee may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and Imperial College will allow the appropriate regulatory authorities direct access to source documents to confirm this verification if necessary. The study site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms / Electronic Data Record

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record on the Imperial INFORM database or both. A CRF is required and should be completed for each included subject.

The investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialled and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts. In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), the study records must be transferred to a designee acceptable to the sponsoring institution, such as another investigator. The investigator must obtain the sponsors written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Independent Ethics Committee & NHS R&D approval

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, Molecular Profiling Supplement, informed consent forms, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IEC/NHS R&D. All correspondence should be retained in the Investigator File.

The only circumstance in which an amendment may be initiated prior to IEC/NHS R&D approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IEC/NHS R&D and Sponsor in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IEC/NHS R&D before use.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH Good practice

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new

information which might influence the evaluation of the benefits and risks of the investigational product, Imperial College and Pfizer should be informed immediately.

In addition, the investigator will inform Imperial College and Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial

End of Trial is defined as the time at which:

- Enrolment is completed according to protocol planned sample size, and assessments and requirements are completed as per protocol.
- The stated objectives of the trial are achieved.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of Imperial College sponsor decision, regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of Axitinib in patients with advanced metastatic colorectal cancer whose disease has progressed on/after or are intolerant to one prior anti-angiogenic therapy at any time.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfils its commitment to publicly disclose the results of studies through posting the results of this study on ClinicalStudyResults.org. Pfizer posts the results of studies that fall into either of the following categories:

- Studies that Pfizer registered on www.clinicaltrials.gov, (ClinicalTrials.gov) regardless of the reason for registration; OR
- All other studies for which the results have scientific or medical importance as determined by Pfizer.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products already approved in any country and for studies that do not involve a Pfizer product, Pfizer posts results within one year after study completion, defined as last subject, last visit (LSLV)
- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within one year after the first regulatory approval of the product
- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year after such discontinuation

Pfizer's posting on ClinicalStudyResults.org includes the following elements:

- Protocol title, study phase, and indication
- A link to approved product labelling, if applicable
- The synopsis of study results
- Citations of known study publications
- Legal disclaimer

The study results synopsis posted on ClinicalStudyResults.org (called the PhRMA website synopsis) uses the format established by the ICH-E3 Clinical Study Report (CSR) Synopsis. If posting of study results to ClinicalStudyResults.org jeopardizes a planned publication of the study results, a Pending Full Publication notice is substituted for the synopsis until the study results publication has issued or two years have elapsed, whichever occurs first.

Pfizer posts citations only for publications that are accessible in recognized (searchable) publication databases. Single-centre results publications for a multi-centre study are generally not posted because they may not accurately reflect the results of the study.

15.2. Publications by Investigator

Pfizer has no objection to publication by Investigator in conjunction with the sponsor, Imperial College of any information collected or generated by Investigator, whether or not the results are favourable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer the opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days. Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. References

1. UK CR. Bowel cancer - survival statistics.
2. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 2006;244(2):254-9.
3. Cancer Research UK Statistics 2011.
4. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350(23):2335-42.
5. Jain RK. Lessons from multidisciplinary translational trials on anti-angiogenic therapy of cancer. *Nat Rev Cancer* 2008;8(4):309-16.
6. Leen E, Goldberg JA, Angerson WJ, McArdle CS. Potential role of doppler perfusion index in selection of patients with colorectal cancer for adjuvant chemotherapy. *Lancet* 2000;355(9197):34-7.
7. Averkiou M, Lampaskis M, Kyriakopoulou K, Skarlos D, Klouvas G, Strouthos C, et al. Quantification of tumor microvascularity with respiratory gated contrast enhanced ultrasound for monitoring therapy. *Ultrasound Med Biol*;36(1):68-77.
8. Gauthier TP, Wasan HS, Muhammad A, Owen DR, Leen EL. Assessment of global liver blood flow with quantitative dynamic contrast-enhanced ultrasound. .J Ultrasound Med. 2011 Mar;30(3):379-85.)

Appendix 1 Required laboratory tests

Laboratory Test	Conventional Units	Conversion Factor	SI Units
Hematology			
hemoglobin (Hgb)	g/dL	x 10	µg/L
platelet count (Plt)	$10^3/mm^3$	x 10^9	10^{12}/L
white blood count (WBC)	$10^3/mm^3$	x 10^6	10^9/L
white blood cell differential	%	x 0.01	fraction
Chemistry			
total bilirubin	mg/dL	x 17.1	mmol/L
alanine transaminase (ALT)	U/L	N/A	U/L
aspartate transaminase (AST)	U/L	N/A	U/L
alkaline phosphatase	U/L	N/A	U/L
gamma-glutamil-transpeptidase (GGT)	U/L	N/A	U/L
lactate dehydrogenase (LDH)	U/L	x 0.016667	µkat/L
total protein	g/dL	x 10	g/L
albumin	g/dL	x 10	g/L
sodium	mEq/L	x 1.0	mmol/L
chloride	MEq/L	x 1.0	mmol/L
potassium	mEq/L	x 1.0	mmol/L
calcium	mg/dL	x 0.25	mmol/L
phosphate	mg/dL	x 0.323	mmol/L
blood urea nitrogen (BUN)	mg/dL	x 0.357	mmol/L
creatinine	mg/dL	x 88.4	µmol/L
glucose	mg/dL	x 0.055	mmol/L
TSH	µU/mL		
free T3	pg/dL		
free T4	pg/dL		
Hepatocellular carcinoma tumor marker			
α-Fetoprotein	ng/mL	x 1.0	µg/L
HBV panel, HCV antibodies			
HBsAg, HBe and anti-HBc	**N/A**		
Anti-HCV antibodies	**N/A**		
Coagulation			
Prothrombin Time (or INR)	secs (or NA)	N/A	secs (or NA)
Urinalysis			
Urine protein, glucose, blood	N/A	N/A	N/A

Appendix 2 Patient Information Sheet

Imperial College Healthcare NHS Trust

Imperial College London

Study title:	**AXMUS-C**
Protocol Number:	
Patient Name:	
Doctor Directing Research:	Dr Harpreet Wasan, Consultant and Reader in Oncology
Doctor Telephone Number:	020 8383 8364 / 3020 or 0208 383 3057

PART 1

Invitation to take part

We would like to invite you to take part in the AXMUS-C research study with the experimental drug **Axitinib**. Before you decide whether or not to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, including your GP if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part

Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The purpose of this study is to test whether an experimental drug called Axitinib is effective in treating patients with advanced colorectal cancer. Axitinib is a type of targeted cancer therapy (chemotherapy) known as a vascular endothelial growth factor inhibitor. The aim of this study is to see if patients who are no longer benefitting from conventional chemotherapy benefit from Axitinib. We will monitor the effect of Axitinib through changes in liver blood flow using a new type of bedside scan called contrast enhanced ultrasound.

The study will examine the side-effects and potential benefits of Axitinib. Previous studies have already been carried out, to check the safety of Axitinib, comprising over 3000 patients. You are being invited to take part in a follow on study which will involve 50 patients. If Axitinib appears to be an effective treatment then the study may continue to recruit more patients.

Why have I been invited?

You have been invited to take part in the study because you have previously been treated with multiple chemotherapy drugs, but these drugs are no longer controlling your disease. If you cannot participate in this study the reasons behind this will be discussed with you by your doctor.

Do I have to take part?

No, taking part in this study is entirely voluntary. It is up to you to decide whether or not to take part. We will describe the study and also go through this information sheet which you can then keep. We will ask you to sign and keep a copy of the consent form to show you have agreed to take part. If you decide to take part you are still free to withdraw at any time, without giving a reason. This will not affect the standard of care you receive. If you withdraw from the study you will have to discontinue the study treatment. Your study doctor will be able to discuss other possible treatment options with you if these are available.

What will happen to me if I take part?

This is a randomised study which means that the selection of patients who will receive Axitinib is entirely random. 2 out of 3 patients in the study will receive Axitinib and 1 out of 3 will receive a placebo (dummy pill). The study is designed in this way so that we can compare whether Axitinib is better (or worse) than a placebo. This study is also 'double–blind'. This means that neither you nor your doctor will know which treatment group you are in (although if your doctor needs to find out he/she can do so in the interest of your safety).

Screening Visit (Before starting study treatment)

Before you can enter the study, your doctor will need to ensure that you are eligible and that it would be safe for you to receive both Axitinib and the contrast enhanced liver ultrasound scans. You may need to undergo some additional blood and urine tests. Your doctor or research nurse will be able to explain any additional tests or hospital visits that are required. In addition, if your last CT scan is more than 28 days old you will be asked to have

another CT scan prior to starting the trial. You will be asked to sign the written consent form for the study before having any study-related tests or scans.

Baseline Visit (On first day of study treatment)

Before you receive the first dose of Axitinib you will need to attend the hospital to undergo baseline tests which can be performed at either Screening or Baseline visit, these will involve:

- An examination by a doctor
- Measurement of height and weight
- An electrocardiogram (heart tracing)
- Measurement of blood pressure, pulse and temperature
- Blood tests (about 6 teaspoons in volume)
- Urine test
- Pregnancy test (if applicable)
- You will be asked what medication (if any) you are taking
- Your study doctor will ask for your permission for tissue from a previous tumour biopsy which has been stored, to be sent for review by a pathologist (a doctor who specialises in tissue analysis).

We will perform a new type of liver ultrasound called contrast enhanced ultrasound. **You will need to avoid food and drink for four hours before the time of your appointment.** We will place an IV (intravenous) cannula (small plastic tube) into your forearm. This can be slightly uncomfortable and is similar to having a blood test. We will administer a licensed medication called SonoVue into the cannula whilst we perform an ultrasound (jelly scan) of your abdomen. We will also examine a control blood vessel in either the neck or groin to check the input of the Sonovue. The examination takes approximately 15 minutes from start to finish. SonoVue allows us to see the pattern of tumour blood flow. This helps us monitor whether Axitinib is working, as we believe it reduces cancer blood flow. This cannot be done effectively without the use of SonoVue. The results are not available straight away as they require computerised image analysis.

Your treatment will start at your baseline visit. You will receive Axitinib or placebo tablets to take twice daily at home.

Treatment Cycles

The study medications will be given in 'treatment cycles' of 8 weeks. After completing the first cycle, you will be offered to continue to take the study medication as long as your disease does not get worse, you do not develop side-effects that would require stopping the study medication and you continue to be eligible for the study. Your study doctor will follow your progress during the study and perform tests and scans. Depending on the results of

these, he may have to change the dose or withdraw you from the study if he feels it is in your health interests. Your doctor will be able to discuss the results of any tests you have during the course of the study.

The following information tells you what will happen at each of the follow up visits:

Day 2, 3 or 4 (optional single visit)

If you give your consent we would like to repeat the contrast enhanced liver scan after 2 to 4 days, as the effect of taking Axitinib may be detectable this early. At this time, we will also perform measurements of pulse, blood pressure and urine. This whole visit is not compulsory.

2 weeks

We will perform an assessment of your symptoms, physical examination, pulse and blood pressure, blood and urine tests and contrast enhanced liver ultrasound. After this visit we may adjust the dose of Axitinib that you are taking. To assess blood levels of Axitinib in your blood we will need to do blood tests at 1 hour, 2 hours and 4 hours after your dose.

4 weeks

We will repeat the procedures performed at 2 weeks but need not perform the contrast enhanced ultrasound scan.

8 weeks (end of cycle 1)

We will repeat the procedures in the baseline examination, including physical examination, blood and urine tests, Axitinib blood levels tests, contrast enhanced liver ultrasound and a CT scan.

Additional visits if treatment is continued

If you benefit from Axitinib during the first 'treatment cycle' of 8 weeks we will see you every 4 weeks thereafter to repeat the procedures performed at 4 weeks. We will repeat your CT scan every 8 weeks. This will continue until the point at which you no longer are benefitting from being on the study. If it is not possible for you to attend the clinic for post-study checks then your study doctor's team or research staff may, instead, contact you by telephone, provided you agree to this.

Expenses and payments:

Travel expenses will not be reimbursed for study visits.

What will I have to do?

You will be required to attend the hospital for treatment and assessments, and will need to inform your study doctor or research nurse of any side-effects that you notice whilst in the study. In addition, you will be provided with a home blood pressure monitoring cuff to measure your blood pressure twice a day before taking your dose of Axitinib/placebo. **You will be asked to fast for 4 hours before each study visit so that we can measure the fasting levels of certain substances in your blood and this is also the best way to do the ultrasound tests.**

Axitinib combined with other drugs and/or alcohol may cause serious or even life-threatening reactions. Therefore, you must always discuss the use of alcohol and any drugs (over-the-counter, prescription, vitamins, herbal or dietary supplements) with your doctor before taking them. (If appropriate, you will be required to use appropriate contraceptive measures (described later in this information sheet)).

You will be given a small card that identifies you as a patient taking part in this study. You should carry it with you at all times.

What are the alternatives for treatment?

You are being offered this study as all conventional treatments are no longer working or not suiting you due to side-effects. There may also be alternative research treatments options that are suitable for you. Your study doctor will be able to discuss what options are available to you. These are normally called phase I trials that are testing the effects of new drugs in cancer patients

What are the side-effects of the treatment?

Each person's reaction to chemotherapy is different. Some people have very few side-effects, whilst others may experience more. The side-effects described will not affect everyone. You will be monitored closely for the development of side-effects and if they occur you may receive treatment to help resolve them. If serious side-effects develop the study drug may be stopped. With any drug, unusual, unexpected, or previously unreported side-effects could occur. Therefore, it is important that you report all symptoms and side-effects that you experience as soon as they occur, whether or not you think they are caused by the study drug.

Axitinib is an experimental drug. Possible side-effects that have been noted from some people taking Axitinib are listed below. The side-effects vary from person to person. Side-effects may be a minor inconvenience or may be severe. Many side-effects go away shortly after the study drug is stopped, but in some cases, side-effects may be serious, long-

lasting, and/or permanent and may even cause death. All patients in the study will be closely monitored for the development of any unexpected side-effects.

Information is available from cancer patients who have received Axitinib in previous studies. The most frequently reported side-effects (occurring in more than 20% of people) who received the study drug were:

- Feeling tired (lethargy)
- Diarrhoea
- feeling Sick (nausea) or Loss of appetite
- High blood pressure
- Change in voice
- sore hands and feet
- Weight loss
- Headache
- Cough
- Constipation

The most widely reported serious side-effects (occurring in more than 15 patients in total out of 3595 patients enrolled In Axitinib trials) were:

- Dehydration (from not drinking enough or nausea)
- High blood pressure
- Diarrhoea
- Nausea
- Vomiting
- Blood clot in the lungs (pulmonary embolism)

Side-effects seen with similar types of chemotherapy drugs could also occur with Axitinib. These side-effects include allergic reactions after taking the drug. Your study doctor can tell you more about these side-effects. You should tell your doctor if you suffer these or any other symptoms. Because this is a new medicine, there can be other adverse effects that are not presently known for Axitinib. You could experience serious side effects if you use other drugs and/or alcohol at the same time. You must always speak to your doctor before taking them. If for any reason you become concerned while taking part in the study you should contact your cancer specialist or research team immediately on the number listed on the first page of this leaflet.

What are the possible disadvantages and risks of taking part?

It is possible that no direct health benefits may result during or following completion of this study. There may be some discomfort from the procedures including some bruising or irritation at the puncture site when blood is collected.

The study will require the use of CT scans before treatment starts and at 8 weekly intervals with the treatment cycles. CT scans have X-ray exposure risks associated with them. If you take part in the study you will have a CT scan at 8 weeks and then at 8 weekly intervals if you continue. It is therefore possible that you may have between 2 and 6 CT scans. Normally, if you are not in a clinical trial you would have fewer scans (2 to 4) during your treatment in the same time period. Each of the CT scans would result in a radiation dose similar to that received from 90 years natural background radiation. Exposure to the x-rays used in CT scans does carry a small risk of having another cancer due to the radiation exposure. There is a long latency period (10 to 30 years) for the development of radiation induced cancers and the risk in the near future is very low. Your study doctor or the radiographer conducting the test can explain the risks involved prior to undergoing the procedure.

Ultrasound itself is safe and doesn't have any known side effects. Contrast enhanced ultrasound uses a small volume (around 3 tablespoons) of the intravenous contrast medium SonoVue. The most common side effects of SonoVue are headache (2%), injection site pain (1%), and injection site skin reaction including bruising (2%). Approximately 1 in 7000 patients can have a serious allergic reaction. **You should not have Sonovue if you have had a heart attack or coronary angioplasty within the last month, an artificial heart valve or are pregnant, breastfeeding or allergic to sulphur (e.g. eggs).** Sonovue is not known to interact with any medications. There has never been a reported overdosage of Sonovue.

Risks while pregnant or breastfeeding

Women who are pregnant or breastfeeding are not allowed to take part in this study. It is not known how the study drugs may affect an unborn child. It is therefore important that women who are pregnant or women who plan to become pregnant should not take part in this study. In addition, women should not breastfeed their baby while in this study. Men should not take part if they plan to father a child. Two reliable forms of contraception must be used (two barrier methods) by both male and female patients and their partners during the study and for at least one month after stopping study medicines. The following are considered adequate barrier methods: diaphragm, condom (by the partner), or sponge. Other methods of contraception such as copper intrauterine device or spermicide may be used. Hormonal contraceptives (oral, injection or implant contraception) are also suitable. Your study doctor can give you advice on this. Women of childbearing potential will be asked to have a pregnancy test before the start of treatment in this study.

If you become pregnant during the course of this study, treatment with study drugs will be immediately stopped. Your study doctor will stay in contact with you until the end of the pregnancy. If you (or your partner) become pregnant during the study, you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy.

If your study doctor discovers during the study that you have another medical condition e.g. high blood pressure, of which you were previously unaware you will be referred to the appropriate doctor for treatment of this condition.

What are the possible benefits of taking part?

If the study drug is effective then you may benefit from its effects on the cancer. However it is possible that there may be no benefits. The information we get from this study will also help us to better advise future patients with colorectal cancer o how to use these type of drugs.

What happens when the research study stops?

Once you have completed one cycle of treatment, you may be able to receive further cycles of study treatment if your study doctor feels this is in your best interest. After you have completed the study your study doctor may decide that Axitinib should continue or that another form of treatment is preferable.

Your study doctor, Imperial College, London or Pfizer may have to withdraw you from the study if your medicine needs to be changed, if it is thought unsafe or inappropriate for you to continue or for administrative reasons. Your study doctor may also withdraw you from the study if you find it difficult to comply with the requirements of the study. Again, your future medical treatment would not be affected. Your study doctor may ask you to have some end of study tests which would normally have been done at the final study visit. If you leave the study, information about you that was collected prior to your withdrawal will continue to be used.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in this study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

Contact Details

If you should have questions about any of the information in the information sheet please address them to the study doctor(s) or the research team mentioned on the first page of this information sheet.

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Patient Information Sheet Part 2: AXMUS-C

What if new information becomes available?

Sometimes during the course of research, new information becomes available about the treatment/drug that is being studied. If this happens, your cancer specialist will tell you about it promptly and discuss with you whether you want to continue in the study. If you decide to not to carry on, your cancer specialist will make arrangements for your general care to continue. If you decide to continue in the study you will be asked to sign a new consent form. Your research doctor might also consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons for this and arrange for your general care to continue. If the study is stopped for any other reason, you will be told why, and your continuing care will be ensured.

What will happen if I don't want to carry on with the study?

Your cancer specialist will ask you if you wish to withdraw from the study altogether or whether you are willing to be contacted for follow-up information.

What if there is a problem?

If you have a concern about any aspect of this study, you should contact your study doctor whose number is on the first page of this information sheet, and he/she will do his/her best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the Patient Advice and Liaison Service based at Charing Cross Hospital, 369 Fulham Palace Road, London, W6 8RF.

What if I come to harm?

Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Dr Harpeet Wasan, 020 8383 8364). The normal National Health Service complaint complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.

Will my taking part in this study be kept confidential?

Unless required by law, only government drug regulatory authorities and your doctor will have access to your medical notes. Under direction of your doctor, authorised representatives of Pfizer and the Independent Ethics Committee can see parts of your medical notes relevant to the clinical study. Clinical data about you may also be sent to Pfizer which is based in the USA where data protection laws are not as comprehensive as in the European Union. Such data may also be seen by government drug regulatory authorities. Information may also be processed by a central laboratory as needed by the study. This information will be treated in the strictest confidence. Your name will not be shown on any forms sent to Pfizer. Your GP will be informed that you are taking part in this study with your permission.

What will happen to the results of the study?

We will analyse the clinical data during and after the trial to assess the drug and to produce reports. The results will be published in the scientific press and may be submitted to government authorities to allow the medicine to be used by other doctors. Any information about you, which leaves the hospital/surgery, may include your initials and date of birth but not your full name or address. Such data may also be seen by government regulatory authorities. **Any reports or publications in medical journals resulting from the study will be anonymous.**

Who is organising and funding the research?

Dr Wasan proposed the study with Professor Leen at Imperial College, London to Pfizer, the drug company that makes Axitinib. Pfizer have provided funds for this study. Imperial College, London is the sponsor and will receive payment from Pfizer to run the study.

Who has reviewed the study?

The study has been reviewed by an independent panel called a Research Ethics Committee, Imperial College, London, the NHS Research & Development office and an expert patient.

Contact for further details

Your cancer specialist should have answered all of your questions. If you have additional questions during the course of this study about the research or your rights as a research patient, you may address them to the study doctor(s) mentioned on the first page of this information sheet. Please contact the study doctor in the event of the following occurring:

a) a new illness or a possible study related injury
b) if you feel different in any significant way
c) if you are admitted to hospital
d) if you are seen at an Accident & Emergency department for any reason

This completes part 2 of the information sheet. If you would like to participate in AXMUS-C we will ask you to read and sign the informed consent form.

Appendix 3 Informed Consent Form

Patient Identifier:

Name of Principal Investigator: Dr Harpreet Wasan, Consultant Oncologist, Imperial College NHS Trust

Please Initial Box

1. I confirm that I have read and understood the information sheet Version 1.0, dated 12/10/2011 for the AxMUS-C study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Imperial College London, Pfizer or regulatory authorities. I give permission for these individuals to have access to my records. ☐

4. I understand that information about me arising from my participation in this study will be processed by the study team at Imperial College London. This information may include my initials and date of birth but not my full name or address. The study team will: ☐
    i. Analyse my clinical data during and after the trial, to assess the drug and to produce reports,
    ii. May send clinical data to Pfizer's parent company in the USA where data protection laws are not as comprehensive as in the European Union, for central analysis. Such data may be seen by government regulatory authorities,
    iii. Hold my data on file and send it to government regulatory authorities in accordance with the government's requirements for clinical trials.

5. I agree to my GP being informed of my participation in the study. ☐

6. I agree to take part in the above study. ☐

7. I agree to have the **optional** contrast enhanced liver ultrasound after 48 hours.

8. I agree for my tumour biopsy (already taken previously) to be sent for tissue analysis ☐

…….	…….	…….
Name of PATIENT (Please Print)	*Signature of PATIENT*	*Date*

…….	…….	…….
Name of WITNESS (Please Print)	*Signature of WITNESS*	*Date*

By signing the consent form, the witness confirms that all the information contained in the PIS/ICF has been read and understood by, the patient or representative, and that informed consent was freely given

CONSENT OBTAINED BY (MUST BE A PHYSICIAN)

…….	……...	……
Name (Please Print)	*Signature of Physician*	*Date*

When completed, 1 for patient; 1 for Investigator file; 1(original) to be kept in medical notes

Appendix 4 GP letter

Study Title:	**AXMUS-C**
Site:	Imperial College Healthcare NHS Trust
Chief Investigator:	Dr Harpreet Wasan, Reader and Consultant in Oncology

Telephone for further information:	0208 383 3057 or 020 8383 8364 /3020

Dear Dr,

Your patient ……. has been diagnosed with metastatic colorectal cancer. Following discussion of treatment options and review of the trial information sheets, (s)he has consented to enter the AXMUS-C study. This is a phase II double-blind, randomised controlled trial comparing Axitinib against placebo in patients with refractory colorectal liver metastases.

Your patient will be randomised to either:

- Axitinib monotherapy

OR

- Placebo

The chemotherapy regimen will be either Axitinib monotherapy or placebo, given as a twice daily tablet starting at 5mg bd and titrating upwards after 2 weeks if required. The initial treatment cycle will be 8 weeks in duration before restaging. At this point your patient may or may not continue based on whether they respond to treatment to the point of disease progression.

The common side effects include lethargy, diarrhoea, sickness, high blood pressure, loss of appetite, change in voice, hand-foot syndrome, weight loss, headache, cough and constipation. Other rare side-effects or allergic reactions may occur and we encourage you to report these to the study team by telephone (phone number below).

Concomitant medications are allowed during this trial, with the exception of **omeprazole** (lanzoprazole is allowed). Axitinib may potentiate the effect of warfarin and INR should be closely monitored. If you have any questions about the trial or concerning specific toxicities arising in your patient, please contact:

Dr H Wasan, Consultant Oncologist and Reader, Tel: 0208 383 3057

Beate Poppinga-Scholz, Team Leader Clinical Trials, Tel: 0208 383 8364/ 3020

Attached is a summary of the trial and a copy of the patient information sheet for your information.

Yours sincerely,

Dr Harpreet Wasan

AXMUS-C Principal Investigator

Trial summary

AXMUS-C (AXitnib Monotherapy Ultrasound in Colorectal cancer) is a double blind, randomised, 2 arm, phase II trial to identify if responders to Axitinib have greater overall survival than Axitinib non-responders and the placebo groups. Both arms commence with 8 weeks of either Axitinib monotherapy or placebo. Response will be judged using an imaging biomarker called the contrast enhanced ultrasound hepatic perfusion index.

Axitinib is a tyrosine kinase inhibitor against vascular endothelial growth factor receptors. It is administered orally at an initial dose of 3mg b.d. which can be titrated upwards to a maximum dose of 10mg b.d..

50 patients with metastatic colorectal cancer who are fit for Axitinib chemotherapy will be randomised at the start of chemotherapy to receive **initially**:

Arm 1: Daily Axitninib treatment for 8 weeks (2/3rds of patients)

OR

Arm 2: Daily placebo treatment for 8 weeks (1/3rd of patients)

The primary outcome measure will be overall survival in the patients whose liver blood flow measured by a special ultrasound test is changed by Axitinib. Secondary outcome measures include progression-free survival, overall response rate and toxicity.

Appendix 5 Liver Ultrasound Protocol

The contrast agent used is SonoVue (Bracco SpA, Milan, Italy), which consists of a phospholipid shell containing the inert gas sulphur hexafluoride. The agent is prepared immediately prior to the examination by mixing 25 mg of the lyophilised powder with 5 ml of saline. 2.4 ml of the preparation is injected as an intravenous bolus via an antecubital vein.

After 4 hours of fasting, DCE-US scan is performed on each subject in the supine position using an iU22 ultrasound scanner (Philips Healthcare, Andover, MA) with a C5-1 curvilinear transducer. The probe is held still in the right intercostal space in order to visualise the porta hepatis. This allows simultaneous visualization of the hepatic artery (HA) and portal vein (PV) at a low mechanical index (0.06) imaging with non-linear pulse sequence in the form of power modulated pulse inversion. A 1 minute contrast/B-mode side-by-side cine loop is recorded with data acquisition starting immediately after the contrast bolus injection. A reading from a control artery (carotid or femoral) is taken to confirm the input function of the test. Cine loops are then transferred to a workstation for analysis.

QLAB software (Philips Healthcare, Andover, MA) is used to quantify contrast dynamics in the HAP and PV. Raw linear DICOM data is used for analysis. Regions of interest of equivalent sizes (5mm^2) are drawn over the HA and PV lumens. Time-intensity curves are obtained by computing the mean intensity of pixels comprised within the regions of interest against time. An example analysis is presented below:

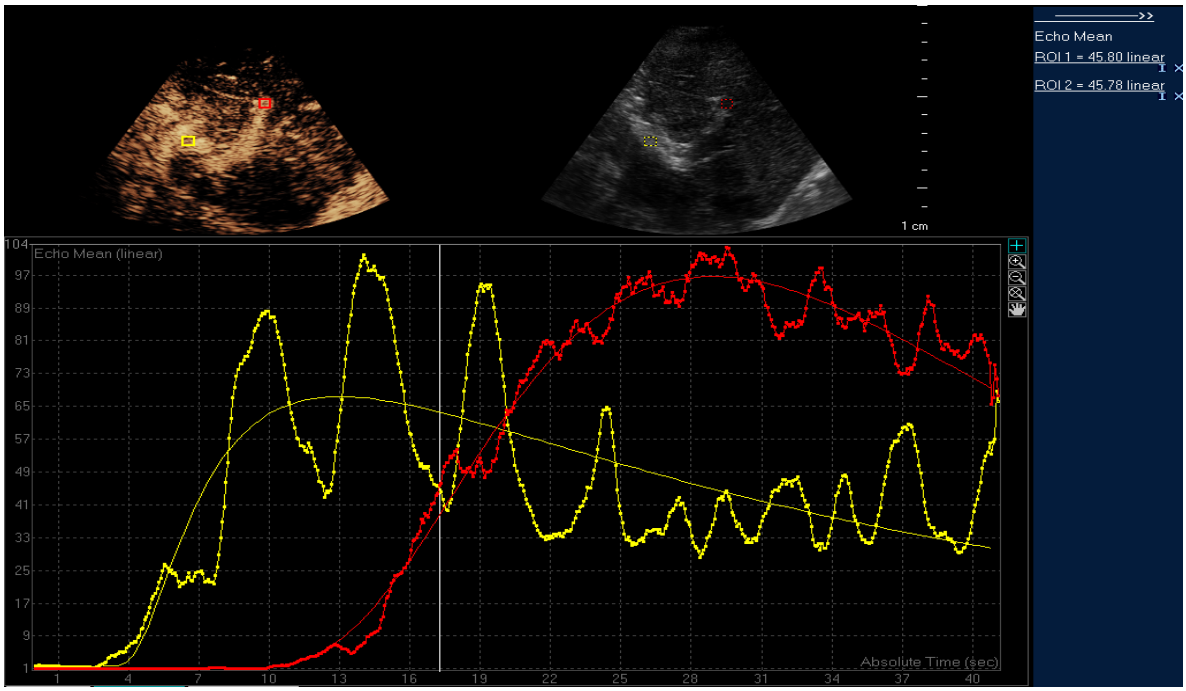


Figure 3: Time-intensity curve for hepatic artery (yellow), portal vein (red) using QLab software. Both have had modelling curves fitted to smooth the data. The calculated values for the DCE-HPI are shown in the box.

TICs are fitted using a least square algorithm based on the Nelder-Mead method (Matlab, The MathWorks, Natick, MA) with a local density random walk function described by:

$$I(t) = AUC\frac{e^{\lambda}}{\mu}\sqrt{\frac{\mu}{(t-t_0)}\frac{\lambda}{2\pi}}exp\left\{-\frac{1}{2}\lambda\left(\frac{\mu}{(t-t_0)}+\frac{(t-t_0)}{\mu}\right)\right\}+I_0$$

AUC is the area under the curve, l^{-1} is the skewness of the curve, m is the travel time between the entry and exit sites of the ROI at the carrier fluid velocity, t_0 is the bolus arrival time, and I_0 is the baseline intensity offset.[12-13] Peak intensity (PI) which correlates with blood volume is defined as max, rise time (RT) is defined as the time taken for the intensity to increase from 5% of PI to 95% of PI, and wash-in slope (WIS) which correlates with blood flow rate[7]. PI and WIS were derived from HA and PV TICs and dynamic contrast-enhanced hepatic perfusion index (DCE-HPI) which reflects the ratio of hepatic arterial to portal venous blood flow to the liver is defined as:

$$DCE-HPI = \frac{PI[HAP].WIS[HAP]}{PI[PV].WIS[PV]}$$

Appendix 6 RECIST Tumour Assessment Criteria (Version 1.1)

The determination of efficacy during this study will be based on objective tumour assessments made according to the RECIST system of unidimensional evaluation.

Measurability of Tumour Lesions

At baseline, individual tumour lesions will be categorized by the investigator as either measurable or non-measurable by the RECIST criteria as described below.

Measurable:

Tumour lesion: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-Measurable: All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with >10 mm to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

NOTE: If measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumour Measurements

All 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 measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesion with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter for all target lesions will be calculated and recorded as the baseline sum longest diameter to be used as reference to further characterize the objective tumour response of the measurable dimension of the disease during treatment. All measurements should be performed using a caliper or ruler and should be recorded in metric notation in centimeters.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent.”

Techniques for Assessing Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical (physical) examination when both methods have been used to assess the antitumour effect of a treatment.

Definitions of Tumour Response

Target Lesions

Complete response (CR) is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial response (PR) is defined as a >30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum longest dimensions.

Progressive disease (PD) is defined as a >20% increase in the sum of the longest dimensions of the target lesions taking as a reference the smallest sum of the longest dimensions recorded since the treatment started, or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the longest dimensions since the treatment started.

Non-Target Lesions

Complete response (CR) is defined as the disappearance of all non-target lesions. All lymph nodes must be non-pathological in size(<10mm short axis).

Non-CR/Non-PD is defined as a persistence of >1 non-target lesions.

Progressive disease (PD) is defined as unequivocal progression of existing non-target lesions, or the appearance of > 1 new lesion.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to differentiate between response or stable disease and progressive disease.

Confirmation of Tumour Response

To be assigned a status of PR or CR, changes in tumour measurements in patients with responding tumours must be confirmed by repeat studies that should be performed ?4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallestmeasurements recorded since the treatment started). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be

reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment. It should also be noted that a tumour marker increase does not constitute adequate objective evidence of tumour progression. However, such a tumour marker increase should prompt a repeat radiographic evaluation to document whether or not objective tumour progression has occurred.

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

Appendix 7 ECOG Performance Status

0 Fully active, able to carry on all pre-disease activities without restriction

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

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

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

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

5 Dead

Appendix 8 Pfizer Reportable Event Cover Sheet

REPORTABLE EVENT COVER SHEET

Use this fax cover sheet to fax a Reportable Event for Investigator-Initiated Research studies.

Include with this form the completed Pfizer Investigator-Initiated Research Serious Adverse Event (IIR SAE) form, CIOMS form or other Pfizer agreed-upon form for SAE reporting. This cover sheet MUST be provided with each completed SAE form. Do not substitute forms/reports or submit additional documentation other than what is required.

Do not fax these forms to any additional fax numbers other than the one listed below.

TO:	***Pfizer Safety PCO OFFICE***	
FAX:		
FROM:		**DATE:**
TELEPHONE:		**FAX:**
NUMBER OF PAGES (INCLUDING COVER SHEET):		
PRODUCT	Axitinib	
PFIZER REFERENCE NUMBER		**EXTERNAL REFERENCE NUMBER**
STUDY TITLE	AxMUS-C	
PATIENT NUMBER		
INVESTIGATOR	Harpreet Wasan, Consultant Oncologist, Hammersmith Hospital, London, UK	

Confidentiality Notice: The documents accompanying this telecopy transmission contain information belonging to Pfizer, which is intended only for the use of the addressee. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this telecopied information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone to arrange for the return of the original documents to us. Thank you.

Investigator Initiated Research
Serious Adverse Event Report Form

For Pfizer internal use only

AER Number	Date Reported to Pfizer

Write all dates as DD/MMM/YYYY

PROTOCOL / STUDY I.D. | CENTER I.D | SUBJECT I.D. / RANDOMIZATION #

Protocol Title:

☐ **Initial Report** ☐ **Follow Up Report** **Country where event occurred:**

Patient Data Initials | Date of Birth | Race ☐ White ☐ Black ☐ Asian ☐ Other | ☐ Male ☐ Female | Weight ☐ lb ☐ kg | Height ☐ in ☐ cm

If patient has died: Date of Death | Cause of Death | Determined by Autopsy ☐ Y ☐ N

Patient History ***Provide relevant medical history below or include copy of the Medical History case report form page. Include other illnesses present at time of event, previous study emergent adverse events, and pre-existing medical conditions. If additional space is necessary, use further copies of this page.***

☐ Check box if a copy of Medical History page of the case report form is included with this report

Disease (specify)	Onset Date	Stop Date	Check box if Ongoing	Pertinent Details *Include surgical procedures and dates*
			☐	
			☐	
			☐	
			☐	

Study Drug, Formulation, Route	*Check box if Pfizer Drug*	Dose	Units	Frequency	Start Date	Stop Date	Check box if Ongoing
	☐						☐
	☐						☐
	☐						☐
	☐						☐
	☐						☐

Concomitant Drugs ☐ None ☐ Unknown ***List below concomitant drugs taken within 2 weeks before the event onset or include copy of Concomitant Drugs case report form page. Exclude all drugs only administered more than two weeks before the event, and any drug used to treat the event or taken after event onset. If additional space is necessary, use further copies of this page.***

☐ Check box if a copy of Concomitant Drugs page of the case report form is included with this report

Drug Name (Trade and Generic)	Reason for Use	Route	Start Date	Stop Date	Check box if Ongoing
					☐
					☐
					☐
					☐
					☐

Relevant Tests ***List only relevant confirmatory test results for event(s), for example, from blood tests, diagnostic imaging. If additional space is necessary, use further copies of this page.***

Test	Date	Result	Units	Normal Range Low	Normal Range High	Comments