CIRCCa

(Cediranib In Recurrent Cervical Cancer)

A Randomised Double Blind Phase II trial of carboplatin-paclitaxel plus cediranib versus carboplatin-paclitaxel plus placebo in metastatic/recurrent cervical cancer

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Dr R P Symonds on behalf of:
National Cancer Research Institute Gynaecological Cancer Group &
Scottish Gynaecological Cancer Trials Group

This study is jointly sponsored by The University of Glasgow and NHS Greater Glasgow and Clyde

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Study Summary

Title: CIRCCa – **C**ediranib **I**n **R**ecurrent **C**ervical **Ca**ncer
A Randomised Double Blind Phase II trial of carboplatin-paclitaxel plus cediranib versus carboplatin-paclitaxel plus placebo in metastatic/recurrent cervical cancer.

Design: Late phase II randomised placebo controlled trial.

Aims: To provide preliminary evidence regarding whether the addition of cediranib to a combination of carboplatin and paclitaxel will increase progression free survival by 50% in patients with metastatic recurrent cervical carcinoma.

Outcome Measures: Progression free survival (primary outcome measure). Also overall survival, response rate, toxicity and quality of life.

Population: 80 patients with histologically proven carcinoma of the cervix, presenting as stage IVb with extra pelvic metastases or relapsing following hysterectomy or radical radiotherapy.

Eligibility: Inclusion Criteria

Patients will be eligible for the study if the following criteria are met:

- Female and over 18 years of age.
- ECOG performance status 0 or 1.
- Written Informed Consent
- Histologically proven carcinoma of the cervix (squamous, adenocarcinoma or adenosquamous mixed).
- Either:
  1. Persistent or relapsed inoperable disease after radical radiotherapy within the irradiated pelvis **or**
  2. Relapse after radical hysterectomy (after radical radiotherapy to pelvis if appropriate) **or**
  3. Extra pelvic metastases **or**
  4. Stage IVb disease at diagnosis
- Patient not suitable for potentially curative surgical procedure.
- Measurable disease in at least one marker site.
- Adequate haematological function, as follows:
  Haemoglobin $\geq$ 10g/dl
  Neutrophils $\geq$ 1.5 x 10^9/l
  Platelets $\geq$ 100 x 10^9/l
  Calculated Creatinine Clearance $\geq$ 35mls/min (measured by EDTA)
- Adequate biochemical function, as follows:
  Bilirubin $\leq$ 1.5 x ULN
  ALT or AST $\leq$ 2.5 x ULN (or ≤5 x ULN if hepatic metastases present)
  Alkaline Phosphatase $\leq$ 2.5 x ULN (or ≤5 x ULN if hepatic metastases present)
- Adequate coagulation, as follows:
  Prothrombin ratio (PTR) / INR ≤ 1.5 or
  PTR / INR between 2.0 and 3.0 for patients on stable doses of anticoagulants
  Partial thromboplastin time <1.2 x control
- Life expectancy >12 weeks

Exclusion Criteria

Patients will be excluded from the study in the following circumstances:

- They have received prior chemotherapy, except cisplatin administered along with radiotherapy as primary treatment.
- Relapse is confined to the pelvis after radical surgery in circumstance where radiotherapy or chemoradiotherapy would be appropriate.
- Relapse is potentially treatable with exenterative surgery.
- History of nervous or psychiatric disorder that would prevent informed consent and compliance
- History of prior malignancy within the previous 5 years except for successfully treated basal cell skin cancer or in-situ breast cancer
- Pregnant or lactating women.
- Fertile woman of childbearing potential not willing to use adequate contraception (oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) for the study duration and at least six months afterwards
- Evidence of uncontrolled infection. (Defined as infection that cannot be resolved readily with antibiotics prior to patient entry into the trial for e.g. pelvic collection)
- History of pelvic fistulae.
- Sub-acute or acute intestinal obstruction.
- Major surgery within 28 days or anticipated while on study.
- Significant traumatic injury during 4 weeks preceding the potential first dose of cediranib.
- Non-healing wound, ulcer or bone fracture.
- Active bleeding.
- History or evidence of thrombotic or haemorrhagic disorders.
- History of inflammatory bowel disease.
- Proteinuria > 1+ on dipstick on two consecutive dipsticks taken no less than 1 week apart, unless urinary protein is <1.5g in a 24 hour period.
- Significant cardiovascular disease (arterial thrombotic event within 12 months, uncontrolled hypertension or angina within 6 months, NYHA grade 2 congestive cardiac failure, grade ≥ 3 peripheral vascular disease or cardiac arrhythmia requiring medication). Patients with rate-controlled atrial fibrillation are eligible.
- Prolonged QTc (corrected) interval of >470ms on ECG or a family history of long QT syndrome.
- CNS disease (brain metastases, uncontrolled seizures or cerebrovascular accident/transient ischaemic attack /subarachnoid haemorrhage within 6 months).
- Any unresolved toxicity ≥ CTC Grade 2 from previous systemic anti-cancer therapy except haematological toxicity (see inclusion criteria "Adequate haematological function") and alopecia.
- A history of poorly controlled hypertension or resting BP>150/100 mmHG in the presence or absence of a stable regimen of anti-hypertensive therapy (measurements will be made after the patient has been resting supine for a minimum of 5 minutes. Two or more readings should be taken at 2 minutes intervals and averaged. If the first two diastolic readings differ by more than 5mmHG, then an additional reading should be obtained and averaged).
- Requiring intravenous nutritional support.
- History of significant gastrointestinal impairment, as judged by the

Investigator, that would significantly affect the absorption of cediranib.
- History or clinical suspicion of spinal cord compression.
- Pre-existing sensory or motor neuropathy ≥ grade 2.
- Known hypersensitivity to carboplatin or paclitaxel
- Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contra-indicates the use of an investigational drug or puts the patient at high risk for treatment-related complications
- Patients who have been treated with potent inhibitors of CYP3A4 and 2C8 such as amiodaraone, clarithromycin, erythromycin, simvastatin, atorvastatin, lovastatin, montelukast sodium, verapamil, ketoconazole, miconazole, indinovir (and other antivirals) and diltiazem within 2 weeks of the first planned dose of cediranib will be excluded [NB These drugs should also not be used during trial period]

Treatment: Carboplatin, AUC 5, q 3-weekly
Paclitaxel, 175mg/m², q 3-weekly
Cediranib or placebo, 20mg o.d.
Maximum of 6 cycles.

Duration: Treatment every 3 weeks, for a maximum of 6 cycles, patients with CR, PR or SD following completion of 6 cycles will continue on cediranib or placebo until progression/toxicity.

Schedule of Events / Investigations

Study Procedures	Screening	Treatment Cycle (1-6)										End of Trmt	Follow Up						
	-28 to -1	D1 C1	D2-D7 C1	D8 C1	D15 C1	D1 C2	D8 C2	D1 C3	D1 C4	D1 C5	D1 C6	+4 weeks	+2 M	+4 M	+6 M	+8 M	+10 M	+12 M	Every 2M until end of year 3 [12]
Informed Consent	X																		
Demographics, medical history, height	X																		
CT/MRI [1]	X							X[2]		X[2]		X	X	X	X	X	X	X	X
Vital Signs (including BP)[3]	X	X	X*	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X				X		X	X	X	X	X	X	X	X	X	X	X	X
Full Blood Count [4]	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
PTR, INR, PTT [5]	X																		
Biochemistry [6]	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Clinical Exam including weight[7]	X	X				X		X	X	X	X	X	X	X	X	X	X	X	X
GFR[8]	X																		
QoL	X					X		X	X	X	X	X	X	X	X	X	X	X	
Toxicity Assessment	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Thyroid Function Tests (Free T3, T4 and TSH)	X							X		X			X	X	X	X	X	X	X
Urinalysis[9]	X	X				X		X	X	X	X	X	X	X	X	X	X	X	X
ECG[10]	X																		
Plasma Blood Samples [11]	X	X		X	X	X	X	X	X	X	X	X	X	X	X				

(1) CT abdo, chest, pelvis is the minimum investigation, in order to assess disease more thoroughly MRI may be required – investigators decision. CT or MRI should be performed every 2 months during 1st year of follow-up until disease progression confirmed. Thereafter in subsequent years of follow-up if patient has not had disease progression, only as clinically indicated i.e. disease progression suspected.

(2) If appropriate this should be carried out within the preceding week prior to the start of the cycle to assess response

(3) Blood pressure monitoring must be performed at screening, D1, D8, D15 of Cycle 1 and at all other time points specified on schedule of events/investigations. *For patients with a previous history of hypertension it is requested the patients GP checks the patients blood pressure during the 1st week of treatment at some point between D2 and D7.

(4) Including haemoglobin, neutrophils, and platelets. Please note screening bloods require to be within 7 days of randomisation.

(5) Coagulation (PTR, INR, PTT) required at baseline.

(6) Urea and electrolytes, liver function tests, serum calcium Please note screening bloods require to be within 7 days of randomisation

(7) Full clinical examination including at baseline, pelvic examination, vaginal and rectal examination if appropriate, and as required at all other times.

(8) GFR measured using isotope test such as labelled EDTA clearance

(9) Urinalysis requires to be checked before each cycle of treatment and at each follow up visit while patients remain on maintenance treatment of cediranib/placebo.

(10) Required at baseline, then as clinically indicated.

(11) Plasma blood samples for VEGFR 2 levels . Translational aspect of protocol which is optional to patients.

(12) Prior to progression, patients should be followed up 2 monthly until end of year 3, every 6 months during years 4 and 5 and yearly thereafter. After disease progression is documented, patients should be followed up 6 monthly during the first 5 years after randomisation and yearly thereafter.

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1 INTRODUCTION

1.1 Background

Although the incidence of cervical cancer has fallen in the UK [1], this tumour is still the second most prevalent female cancer in the world [2]. The treatment for those patients who develop metastatic disease or relapse within the irradiated pelvis is very unsatisfactory. Cisplatin, either alone or in combination, produces response rates of between 20 to 30%. Overall the survival is less than 10 months [3, 4, 5, 6].

In the recent Gynaecological Oncology Group trial 204, the survival curves for patients treated with four different cisplatin doublets (topotecan, paclitaxel, vinorelbine or gemcitabine combined with cisplatin) were superimposable and response rates varied between 23 and 28% [7]. Most patients who relapse or develop distant metastases after radiotherapy have already received cisplatin during initial chemoradiotherapy. For this reason a non-platinum combination (docetaxel and gemcitabine) was chosen for the Scottish Gynaecological Cancer Trial Group's SCOTCERV1 regimen. However the response rate for this trial was only 30%. Tumour vascularity has been shown to be a potential target in the treatment of cervical cancer. High tumour angiogenesis is associated with poor survival when cervical cancer is treated by radiotherapy [8] and high tumour vascularity is a significant prognostic factor which is independent of intrinsic tumour radiosensitivity [9]. Epithelial growth factor receptor (EGFR) [10] or vascular endothelial growth factor receptor (VEGFR) [11] are both potential therapeutic targets. In particular high levels of intratumoral VEGF has been correlated with a higher stage at diagnosis, more lymph node metastases and a poorer outcome [11]. The worse outcome associated with high VEGF is an independent prognostic factor which is independent of tumour stage as shown in multivariate analyses of poor prognostic factors after radiotherapy [12]. The increased production of VEGF within cervical tumours is multi-factorial. Cervical cancers usually contain hypoxic areas, a powerful stimulus for expression of hypoxia inducible factor (HIF-1) which in turn leads to increased VEGF expression [13]. Virtually all cases of cervical cancer are associated with human papilloma virus (HPV) infection. The HPV genome encodes two oncogenes E6 and E7 whose protein products inactivate p53 and pRb respectively impairing normal cell cycle inhibition and allowing proliferation of HPV infected cells. E6 oncoprotein up-regulates production of VEGF [14] and along with E7 oncoprotein down-regulates the angiogenesis inhibitors thrombospondin-1 and maspin [15]. Another reason to favour the anti-VEGF approach is that initial clinical data from EGFR targeted studies, including monoclonal antibodies and small molecules, have demonstrated only modest activity. On the other hand VEGFR inhibitors seem more active with a case report of a complete response [16]. Bevacizumab in combination with 5 Flurouracil showed promising activity in a small series of heavily pre-treated patients [17]. A recently published Gynecologic Oncology Phase II study [18] demonstrated 11% partial response to bevacizumab monotherapy with a median response duration of 6.21 months. All patients received bevacizumab as second or third line treatment. Cediranib (AZ2171) is one of the most potent VEGFR targeted tyrosine kinase (TK) inhibitors and there is now considerable experience with its usage [19]. There is also UK trial experience with this drug, as the experimental arm in ICON-6 (relapsed ovarian cancer) is paclitaxel, carboplatin and cediranib. Paclitaxel and carboplatin has become a widely used treatment for relapsed cervical cancer partly through familiarity with its use in ovarian cancer and partly because of the assumption that it is likely to be of comparative activity to other platinum-based combinations. Although there are no reported randomised clinical trials, encouraging results from retrospective studies support the use of this combination. A response rate of 40% has been reported from Vancouver [20]. In a retrospective comparison of the results of patients treated by either cisplatin and paclitaxel or carboplatin and paclitaxel according to clinicians' preference, the response rate following cisplatin and paclitaxel was 29% compared to 53% for those who received carboplatin and paclitaxel. With a median follow-up of 9 months survival was not dissimilar with a median survival of 14 and 11 months respectively [21].

Cediranib (AZD2171) is a highly potent inhibitor of vascular endothelial growth factor-A signalling. Cediranib acts by inhibiting the tyrosine kinase activity of VEGF receptors [19] thereby disrupting the VEGF signalling pathways in endothelial cells. Cediranib has a high potency against VEGF receptor-2 which is considered to be the predominant signalling receptor for endothelial cell proliferation, differentiation and vascular permeability. Cediranib also has activity against VEGFR-1, VEGFR-3 and c-kit.

Cediranib has high oral bioavailability, absorption is relatively slow with peak serum levels (Cmax) concentrations reached 1 to 8 hours after oral administration. Food can decrease absorption therefore cediranib should be taken 1 hour before or 2 hours after food. Cediranib is excreted both in the faeces and the urine, following extensive metabolism, with the former route predominating. After attaining Cmax, plasma concentrations decline in an apparent bi-exponential fashion with a half life of 22 hours +/- 6.5 hours. Cediranib avidly binds to plasma proteins and after multiple dosings steady state plasma concentrations are achieved after approximately 7 days. Commonly observed toxicities of cediranib are hypertension, fatigue and diarrhoea.

In previous cediranib studies, increases in blood pressure have been observed and cases of hypertension have been reported, including CTCAE grade 4 hypertension and end-organ damage related to hypertension, such as cerebrovascular events. Left ventricular dysfunction, in some cases leading to cardiac failure has been observed in patients receiving cediranib with risk factors for left ventricular dysfunction (including previous or concomitant anthracycline treatment). A number of bleeding events have occurred. Some of these have been fatal but causality could not be unequivocally assigned to cediranib. Fatigue, hand and foot syndrome, diarrhoea, nausea, vomiting and headache are commonly occurring adverse events in cediranib studies. Dehydration has been observed in clinical studies as a consequence of cediranib-related or chemotherapy-related diarrhoea or vomiting; furthermore, chemotherapy associated anorexia, or reduced oral intake may also be the cause. Hoarseness (dysphonia) has been reported as common and dose-related. Muscle weakness, proteinuria, dry mouth and oral mucosal inflammation have been observed in cediranib studies. Reversible posterior leukoencephalopathy syndrome (RPLS) has been observed in patients receiving cediranib in clinical studies. Increases in transaminases and occasional increases in total bilirubin have been seen. Thrombocytopenia (mostly grade 1 or 2) has been seen with both cediranib monotherapy and combination treatment. Also, there is a dose-related trend of increases from baseline in thyroid stimulating hormone (TSH) levels, which may be linked with clinical hypothyroidism.

1.2 Rationale

There is no satisfactory treatment for recurrent cervical cancer following chemoradiotherapy. Platinum based combinations are currently indicated as the standard of care and the balance between clinical benefit and toxicity is important to evaluate in each case. Paclitaxel and carboplatin has become widely used treatment for relapsed cervical cancer partly through familiarity with its use in ovarian cancer and partly because of the assumption that it is likely to be of comparative activity to other platinum based combinations. The combination of paclitaxel and carboplatin is familiar to gynaecological, medical and clinical oncologists and it forms an appropriate control arm in this study. It is therefore proposed that this trial tests the addition of cediranib to this combination (paclitaxel and carboplatin) in patients with metastatic/recurrent cervical cancer. There are currently no competing trials in the United Kingdom or Europe.

The increase in progression-free interval we aim to detect would be from 4 months to 6 months, which is the minimal interval that would be clinically significant.

If a favourable outcome is achieved the aim is to conduct a Phase III study comparing paclitaxel/carboplatin/cediranib to paclitaxel/carboplatin in this group of patients. In addition

it would provide a basis for Phase II/III studies in patients with locally advanced disease receiving primary treatment by radiotherapy and cisplatin.

2 STUDY OBJECTIVES

The primary objective of the study is to provide preliminary evidence regarding whether the addition of cediranib to a combination of carboplatin and paclitaxel will increase the progression-free survival by 50% in patients with metastatic or recurrent cervical carcinoma. The minimum increase in progression free-survival considered clinically significant is from 4 to 6 months.

The secondary objectives are to provide estimates of differences in response, survival, toxicity, quality of life and pharmacodynamic end-points between the study arms.

3 STUDY DESIGN

This study is a phase II randomised placebo control trial of patients who are initially diagnosed with metastatic cervical cancer or subsequently develop metastases or local pelvic recurrence following radical treatment. A total of 80 patients are required. Patients will be randomised to receive either cediranib (20mg daily) or a matched placebo. In addition patients will receive up to 6 cycles of carboplatin (AUC5) and paclitaxel (175mg/m^2) repeated every 3 weeks for up to 6 cycles, at which point the patient will cease all cytotoxic chemotherapy until confirmed progression. Treatment with cediranib or a placebo will be continued until progression or toxicity supervenes. Patients will be assessed for toxicity at each cycle of chemotherapy and will be assessed for response clinically or radiologically after 2, 4 and 6 cycles of chemotherapy respectively. Patients will then be followed-up no less frequently than at 2 monthly intervals. Patients will be assessed clinically for response and toxicity at each clinic visit. Every 2 months during follow-up, patients will have repeat CT scans or MRI scan (whichever is clinically most appropriate) until tumour progression. Once a patient has confirmed progression subsequent treatment is at the investigator's discretion.

3.1 Study Outcome Measures

The primary outcome measure of this study is overall progression-free survival.

The secondary outcome measures are:

- A reduction in plasma VEGFR2 levels from baseline at day 28
- Response to chemotherapy (using RECIST1.1 criteria)
- Overall survival
- Toxicity (assessed using NCI CTCAE v4.0)
- Quality of Life (assessed using EORTC QLQ-C30 and CX24)

4 PARTICIPANT ENTRY

4.1 Pre-registration / randomisation Evaluations

Investigations, such as CT or MRI scans, which have been performed as part of routine clinical practice can be used as part of the screening process, however no other non- routine investigations or tests required for screening may be performed prior to signature of the informed consent form.

The following baseline information should be obtained within 28 days prior to randomisation, with exception of laboratory investigations which require to be within 7 days prior to randomisation:

- Demographic data and medical history including previous and current diseases and medications.
- Baseline toxicity assessment to document pre-existing toxicity from previous treatment (assessed using CTCAE v4.0)
- Full clinical examination including the assessment of height, weight, pulse rate and blood pressure. If appropriate, vaginal and rectal examination. Examination under anaesthetic should be performed if required.
- Biopsy of any readily accessible lesion within the cervix or vagina.
- Evaluation of ECOG performance status.
- Full blood count including haemoglobin, neutrophils and platelets.
- Coagulation: PTR, INR and PTT
- Serum biochemistry including urea and electrolytes, liver function tests, serum calcium and thyroid function tests.
- Isotope test of glomerular filtration rate such as labelled EDTA clearance
- Radiological evaluation of metastatic disease. This should be a minimum of a CT scan of chest abdomen and pelvis. In order to assess pelvic disease more fully patients may also require an MRI scan.
- Urinalysis
- ECG to exclude prolonged QTc
- Plasma blood samples for VEGFR levels. Translational aspect of trial, only to be collected for patients who have consented to this. Please refer to appendices VII for further details for collection of blood samples.

4.2 Inclusion Criteria

Patients will be eligible for the study if the following criteria are met:

- Female and over 18 years of age.
- ECOG performance status 0, or 1.
- Written Informed Consent.
- Histologically proven carcinoma of the cervix (squamous, adenocarcinoma or adenosquamous mixed).
- Either:
  1. Persistent or relapsed inoperable disease after radical radiotherapy within the irradiated pelvis **or**
  2. Relapse after radical hysterectomy (after radical radiotherapy to pelvis if appropriate) **or**
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  4. Stage IVb disease at diagnosis
- Patient not suitable for potentially curative surgical procedure.
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- Adequate haematological function, as follows:
  Haemoglobin $\geq$ 10g/dl
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  Partial thromboplastin time <1.2 x control
- Life expectancy >12 weeks

4.3 Exclusion Criteria

Patients will be excluded from the study in the following circumstances:

- They have received prior chemotherapy, except cisplatin administered along with radiotherapy as primary treatment.
- Relapse is confined to the pelvis after radical surgery in circumstance where radiotherapy or chemoradiotherapy would be appropriate.
- Relapse is potentially treatable with exenterative surgery.
- History of nervous or psychiatric disorder that would prevent informed consent and compliance
- History of prior malignancy within the previous 5 years except for successfully treated basal cell skin cancer or in-situ breast cancer
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- Fertile woman of childbearing potential not willing to use adequate contraception (oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) for the study duration and at least six months afterwards
- Evidence of uncontrolled infection. (Defined as infection that cannot be resolved readily with antibiotics prior to patient entry into the trial for e.g. pelvic collection)
- History of pelvic fistulae.
- Sub-acute or acute intestinal obstruction.
- Major surgery within 28 days or anticipated while on study.
- Significant traumatic injury during 4 weeks preceding the potential first dose of cediranib.
- Non-healing wound, ulcer or bone fracture.
- Active bleeding.
- History or evidence of thrombotic or haemorrhagic disorders.
- History of inflammatory bowel disease.
- Proteinuria > 1+ on dipstick on two consecutive dipsticks taken no less than 1 week apart, unless urinary protein is <1.5g in a 24 hour period.
- Significant cardiovascular disease (arterial thrombotic event within 12 months, uncontrolled hypertension or angina within 6 months, NYHA grade 2 congestive cardiac failure, grade ≥ 3 peripheral vascular disease or cardiac arrhythmia requiring medication). Patients with rate-controlled atrial fibrillation are eligible.
- Prolonged QTc (corrected) interval of >470ms on ECG or a family history of long QT syndrome.
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- A history of poorly controlled hypertension or resting BP>150/100 mmHG in the presence or absence of a stable regimen of anti-hypertensive therapy (measurements will be made after the patient has been resting supine for a minimum of 5 minutes. Two or more readings should be taken at 2 minutes intervals and averaged. If the first two diastolic readings differ by more than 5mmHG, then an additional reading should be obtained and averaged).
- Requiring intravenous nutritional support.
- History of significant gastrointestinal impairment, as judged by the Investigator, that would significantly affect the absorption of cediranib.
- History or clinical suspicion of spinal cord compression.
- Pre-existing sensory or motor neuropathy ≥ grade 2.
- Known hypersensitivity to carboplatin or paclitaxel
- Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contra-indicates the use of an investigational drug or puts the patient at high risk for treatment-related complications

- Patients who have been treated with potent inhibitors of CYP3A4 and 2C8 such as amiodaraone, clarithromycin, erythromycin, simvastatin, atorvastatin, lovastatin, montelukast sodium, verapamil, ketoconazole, miconazole, indinovir (and other antivirals) and diltiazem within 2 weeks of the first planned dose of cediranib will be excluded [NB These drugs should also not be used during trial period]

4.4 Concomitant Medication

Cediranib is highly protein bound and is potentially metabolised by hepatic P_{450} enzyme systems.

Patients who require oral anticoagulants (coumadin, warfarin) are eligible as long as the INR is stable and increased monitoring occurs during trial treatment. Patients may receive low molecular weight heparin while receiving cediranib/placebo, and physicians may prefer to anti-coagulate their patterns with this, rather than warfarin, while they are receiving trial treatment.

There is insufficient data on other concomitant medications that may significantly affect P_{450} drug metabolising activity by way of enzyme induction and inhibition to specifically contraindicate or permit their use. It therefore may be best to avoid the use of very potent inhibitors of CYP3A4 and 2C8 such as amiodarine, clarithromycin, erythromycin, simvastatin, atorvastatin, lovastatin, montelukast sodium, verapamil, ketoconazole, miconale, indinovir (and other antivirals) and diltiazem and inductors such as phenbarbitone, phenytoin, carbamazepine and rifampicin within 2 weeks of the first dose of cediranib/placebo and throughout the trial period.

Patients should be advised to avoid grapefruit juice and St John's Wort which are also hepatic cytochrome P_{450} inhibitors.

Although the dihydropyridine calcium-channel blockers nifedipine and amlodipine are both metabolised via CYP 3A4 these drugs have been used with cediranib in other trials and can be used in the management of cediranib induced hypertension.

Caution should be exercised for patients using any medication that may markedly affect renal function (e.g. vancomycin, amphotericin, ibuprofen, pentamidine). Such medications may, however, be used with caution if deemed essential for treatment of a particular infection or continued if patients are using them prior to commencing the study with no effect on renal function demonstrable on blood or urine testing.

Other medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator.

4.5 Patient Registration and Randomisation

Patients will not be able to be registered/randomised to the study until the site has been activated to begin recruitment to the trial.

Prior to starting treatment and when the patient's eligibility has been confirmed, consent forms and registration forms have been completed, site staff must contact the Cancer Research UK Clinical Trials Unit, Glasgow to randomise the patient to the study. Randomisation to the study can be done by either telephone or fax on the following numbers:

Randomisation Telephone Number: 0141 301 7197
Randomisation Fax Number*: 0141 301 7184
Randomisation Service: Monday- Thursday 08.30-17.00, Friday 08.30-16.30
Fax 24 hours*(Faxes received outside office hours will be dealt with the next working day)

All patients must be registered/randomised onto the study prior to commencement of any treatment.

A minimisation algorithm incorporating a random component will be used to allocate patients to either cediranib or placebo. The factors used in the minimisation will be:-

- Disease site (local relapse only; extra-pelvic metastases only; local relapse and extra pelvic metastases)
- Disease free survival after primary therapy/primary stage IVb ($\leq$12 months v > 12 months v treatment naïve stage IVb)
- Number of lines of previous treatment (0,1)
- ECOG performance status (0,1)
- Investigational site

Each patient randomised will be allocated a unique sequential patient ID number for the study together with a study drug code. On receipt of the sequential patient ID number and study drug code code, site staff will access a computer-based supply management system operated by a commercial organisation, Cenduit who have been contracted on behalf of Astra Zeneca. The site staff will enter the sequential patient ID number, patients date of birth + study drug code to the system which will result in giving details of the allocated drug pack number to be dispensed for the patient being communicated to the site staff, and via email to the Site Pharmacist and CTU personnel.

Site personnel will be able to access the Cenduit system via a secure website, using individual access codes. Full telephone support is available via a toll free telephone number. Study specific user guides and PIN details will be sent to each site after initiation.

The toll free access line for the Cenduit helpdesk is 00 800 1012 1960.

The supply management system (Cenduit) will track Trial Drug supply at each site and will automatically order drug/placebo to maintain adequate stock based on consumption of trial supplies at that site.

4.6 Withdrawal Criteria

The patient can decide to withdraw from the study at any time. The PI also has the right to withdraw patients from the study if he/she feels that it is in the best interests of the patient. Full details of the reasons for withdrawal should be recorded on the relevant Case Report Form (CRF) and patient's medical record. If a patient withdraws during the treatment phase this information should be recorded on the Treatment CRF and the patient's medical record. Withdrawn patients should be followed-up in accordance with the protocol. If a patient withdraws from treatment and withdraws their consent for follow-up, a Consent Withdrawal Form must be completed and retained at the study site. A Consent Withdrawal Notification Form must also be completed and submitted to the Cancer Research UK Clinical Trials Unit.

5 TREATMENTS

5.1 Treatment Arms

The control arm (Arm A) is carboplatin AUC 5 and paclitaxel 175mg/m²repeated every 3 weeks for a maximum of 6 cycles, plus 20mg placebo orally once daily.

The trial arm (Arm B) is carboplatin AUC 5 and paclitaxel 175mg/m²repeated every 3 weeks for a maximum of 6 cycles, plus 20mg cediranib orally once daily.

Patients will be randomised in a double blind fashion to receive either Arm A or Arm B, and treatment with placebo or cediranib will be continued until the patient progresses or toxicity

becomes unacceptable. Neither the patient nor the Investigator will be aware of whether the patient's Trial Drug is cediranib or placebo tablets.

5.2 Specific Drug Information

5.2.1 Trial Drug: Cediranib and Placebo

Cediranib is an investigational medicinal product. It is not licensed for the treatment of cervical cancer or any other cancer, or any indication.

Supplies

- CIRCCa is a double blind trial hence neither the patient nor the investigator will be aware of whether the patient's Trial Drug is cediranib or placebo tablets.
- Trial Drug (cediranib and placebo) will be provided by Astra Zeneca to sites for use by patients in CIRCCa and will be special investigational medicinal product clinical trial stock.
- Trial drug (cediranib and placebo) will be supplied as brown or beige, round, film coated tablets. Active drug and placebo will be identical in appearance, as will be the bottles in which they are provided.
- Cediranib will be supplied as 15mg and 20mg tablets with matching placebo.
- Packaging, labelling and preparation of the Trial Drug (cediranib and placebo) will be performed in a way that will ensure blinding throughout the trial.
- Trial Drug (cediranib and placebo) will be packaged into high-density polyethylene (HDPE) bottles, with child resistant, tamper evident closures. Labelling of the Trial Drug will be performed in accordance with Good Manufacturing Practice and in accordance with local labelling requirements, stating that the Trial Drug is for clinical trial use only and should be kept out of the reach of children. **** Please note that the supplies of investigational medicinal product in this trial will not be labelled as cediranib. Instead supplies will be labelled as AZD2171 xxmg or placebo.****
- Only those supplies intended for use in the study should be dispensed to study participants and clinical trial supplies must be dispensed in accordance with the study protocol.
- Full instructions regarding management, labelling and accountability of Cediranib is given in the IMP Management Document for the study.

Preparation, Administration and Dose Guidelines

- Trial Drug (cediranib/placebo) will be taken from day 1 of cycle 1 of chemotherapy and continued until protocol defined disease progression, toxicity or patient's wish to discontinue.
- The starting dose of cediranib is 20mg orally once daily.
- Tablets should be taken as a single mid-morning dose with approximately 240mls of water with the patient in the upright position.
- Tablets should be swallowed whole and not chewed, crushed or divided.
- Tablets should be taken at least 1 hour prior to the consumption of lunch, and at least 2 hours after breakfast.

- Tablets should be taken around the same time each morning.

- In the event that the patient cannot hold the tablet down (if patient vomits) within 30 minutes after taking the tablet or if the patient can identify the tablet in the vomit content, the patient can re-take the tablet from the bottle.

- If a patient forgets to take a tablet, and it is within 6 hours of the scheduled time then the patient should be advised to take them as soon as possible. If it is more than 6 hours after the scheduled time, then study medication should not be taken for that day. Study medication should continue as scheduled previously on the subsequent day and the missed dose should be returned to the centre at the next visit. A patient should not take more than a single day's dose of tablets, within a day.

- For elective surgery during the trial it is recommended that Trial Drug (cediranib/placebo) is stopped for 2 consecutive weeks prior to the surgical procedure. Trial Drug (cediranib/placebo) can be restarted when the surgical wound has healed.

- Trial Drug (cediranib/placebo) should be stopped as soon as possible if emergency surgery is being considered. Precautions should be taken to minimise the potential risk of bleeding and thrombosis in all patients. It is not necessary to routinely unblind patients who require emergency surgery. Trial Drug (cediranib/placebo) can be restarted when the surgical would has healed.

- If paracentesis or drainage of pleural effusions is required while patients are on Trial Drug (cediranib/placebo) then this should be performed under ultrasound guidance. (If patients clotting and platelets are within normal limits there is not a requirement to stop the Trial Drug.)

- As a precautionary measure, it is recommended that an interval of 2 days is left between the insertion of any central venous access devices (CVADs) and treatment with the Trial Drug (cediranib/placebo). The Trial Drug (cediranib/placebo) may be restarted after 2 days.

5.2.2 Paclitaxel

Pre-medication

- When paclitaxel is being given, prior to commencing chemotherapy give paclitaxel hypersensitivity prophylaxis, including H1/H2 antagonists and corticosteroids, as per local standards, for example:

- 30 minutes prior to paclitaxel
    - Dexamethasone 20mg IV
    - Chlorphenamine 10mg IV (bolus diluted with 5-10ml Normal Saline)
    - Ranitidine 50mg IV/Cimetidine 300 mg IV (in 20ml Normal Saline over 2 minutes)

  This schedule is a suggestion participating centres may vary this according to their standard local practice. The products specified in this schedule will not be considered non-investigational medicinal products (NIMPs)

- Immediately pre-chemotherapy give anti-emetics as per local standards, this may include oral or intravenous $5HT_3$ antagonists.

- Anaphylaxis precautions should be available during infusion for the emergency treatment of hypersensitivity reactions.

- Paclitaxel must be administered prior to carboplatin.
- Hypersensitivity reactions to paclitaxel should be managed according to local protocols. Patients may be retreated at full dose after administration of medication to prevent hypersensitivity reactions unless judged by clinician as severe hypersensitivity reaction in which case local practice should be followed.

Paclitaxel

- Paclitaxel for use in the trial should be taken from usual pharmacy shelf stock, there is no provision for funding, reimbursement or discounted stock.
- Reconstitute and administer via a non-PVC giving set and connectors incorporating a filter ≤ 0.22µm. Non-PVC containing infusion bags should be used.
- Reconstitute paclitaxel 175mg/m^2 (cap at BSA 2.0m^2) in 500ml of N Saline or 5% glucose according to local standard.
- Body Surface Area (BSA) is worked out using a computer algorithm or according to the nomograms as specified in Appendix VI. The BSA should only be recalculated if real body weight changes by more than 10%.
- Give paclitaxel intravenously over **three hours** via a rate controlling device.
- Monitor closely for allergic reactions and cardiac arrhythmias as per local guidelines.

5.2.3 Carboplatin

- Carboplatin for use in the trial should be taken from usual pharmacy shelf stock, there is no provision for funding, reimbursement or discounted stock.
- Reconstitute carboplatin AUC 5, in 250ml of 5% glucose according to local standard practice.
- Give carboplatin intravenously over 30-60 minutes (depending on standard local practice).
- Allergic reactions to carboplatin should be managed according to standard local practice.

Carboplatin Dose

The carboplatin dose should be calculated according to the Calvert formula [22] as follows:

- Carboplatin dose = AUC X (GFR +25)

For the purposes of this protocol a formal measurement of GFR is required, using a isotope test of glomerular filtration rate such as labelled EDTA clearance

If labelled EDTA clearance is unavailable to sites, the site should contact the trials unit for advice on an alternative method for measurement of GFR which may be acceptable to be used.

The GFR should only be re-measured for:

- Renal toxicity (If serum creatinine varies by >25% or if serum creatinine > 1.5 times upper limit of normal [CTC Grade 2])
- Each dose modification of carboplatin

Dose capping of carboplatin may be carried out according to standard local practice.

GFR Limitations

- Isotopic GFR is inaccurate in patients with significant effusions, ascites or oedema as the isotope distributes into third space fluid collections.

- It is assumed that clinicians entering patients into this protocol will be aware of these issues and the clinical judgement of an experienced clinician should be applied to the calculation of the carboplatin dose.

5.3 Trial Treatment Recording

Reasons for any dose delays, dose reductions, dose omissions or stopping chemotherapy treatment and/or Trial Drug should be documented in the appropriate part of the CRF and in the patient's medical record. Tablet counts will be performed at each follow-up visit by pharmacy to assess compliance with Trial Drug (cediranib and placebo).

5.4 Concomitant Therapy

All non-cancer treatments that the responsible physician feels are appropriate are allowed.

Patients should receive full supportive care during and after the administration of chemotherapy, plus Trial Drug (cediranib or placebo). This includes transfusion of blood and blood products and/or the use erythropoeitan and/or G-CSF (as clinically indicated) and antibiotics for infective complications as per local practice. Anti-emetics should be given according to local practice (pre and post chemotherapy). The treatment details should be recorded in the CRF. Anaphylaxis precautions should be observed during administration of carboplatin and paclitaxel as per local practice.

See section 4.4 for important information on concomitant treatment with oral anticoagulants, drugs which may inhibit or induce the hepatic P_{450} enzyme system and drugs which may cause renal impairment.

5.5 Interaction with Other Drugs

The clearance of paclitaxel is significantly reduced when administered after carboplatin. This can lead to an increase in toxicities such as myelosuppression. For this reason paclitaxel must be administered prior to carboplatin.

There are no known interactions between cediranib and carboplatin or paclitaxel.

5.6 Dose Modifications for Toxicity

Carboplatin and Paclitaxel toxicities

Haematological Toxicity
Treatment should be delayed if either of the following occur within 24 hours prior to scheduled therapy:

- Neutrophil count $<1.5x10^9$/l
- Platelet count $<100x10^9$/l

Full blood count (FBC) should be repeated at least weekly until haematological recovery occurs (neutrophil count $1.5x10^9$/l or greater and platelet count $100x10^9$/l or greater). If haematological recovery occurs within 7 days no dose modification is necessary. If haematological recovery occurs beyond 7 days, the doses of carboplatin and paclitaxel should be reduced for all subsequent cycles (see table 1). If the neutrophil count is $<1.5x10^9$/l but with a platelet count of at least $100x10^9$/l there should be no modification of carboplatin dose but paclitaxel dose should be reduced to 135mg/m^2 for all subsequent cycles.

If the platelet count is $<100x10^9$/l with a neutrophil count of at least $1.5x10^9$/l there should be no modification of paclitaxel dose but carboplatin should be reduced by 1 AUC unit to AUC 4 for all subsequent cycles. If the platelets are $<100x10^9$/l and the neutrophils are $<1.5x10^9$/l carboplatin should be reduced by 1 AUC unit to AUC 4 and paclitaxel should be reduced to 135mg/m^2. Patients who fail to recover adequate counts after a delay of 2 weeks or more or have a second dose limiting haematological toxicity to a component of treatment should be withdrawn from protocol chemotherapy treatment (Patients should however continue treatment with cediranib or placebo). If necessary such patients should be discussed with the Chief Investigator or Lead Co-Investigator.

Delay in neutrophil recovery to ≥ 1.5 x 10^9/l	**Delay in platelet recovery to ≥ 100 x 10^9/l**	**Dose modifications**
≤ 7 days	≤ 7 days	None
7-14 days	≤ 7 days	↓ paclitaxel to 135mg/m^2 No change to carboplatin
≤ 7 days	7-14 days	No change to paclitaxel ↓ carboplatin by AUC of 1
7-14 days	7-14 days	↓ paclitaxel to 135mg/m^2 ↓ carboplatin by AUC of 1
> 14 days	> 14 days	Withdraw from protocol treatment

In addition to checking FBC prior to each cycle of chemotherapy it will be checked weekly between cycle 1 and cycle 2. Grade 4 thrombocytopenia identified at any time during treatment with cediranib/placebo will result in a dose reduction of cediranib/placebo from 20mg od to 15mg od.

Renal Toxicity
The combination of carboplatin + paclitaxel, with or without cedirinab, using the schedule previously described, is not directly expected to cause renal toxicity. There are therefore no specific dose modifications for renal toxicity. The administered dose of carboplatin should be recalculated based on a remeasured GFR if there is renal toxicity (If serum creatinine varies by > 25% or if serum creatinine >1.5 times upper limit of normal [CTC Grade 2]). The patient should be removed from protocol treatment if her measured GFR is <35ml/min.

Hepatic Toxicity
If the bilirubin is between the upper limit of normal and 1.5 times the upper limit of normal the paclitaxel dose should be decreased to 135mg/m^2. If the patient is already being treated at 135mg/m^2 then paclitaxel should be stopped.

If the bilirubin is increased >1.5 times the upper limit of normal or transaminase is > 2.5 times the upper limit of normal (without the presence of liver metastases) paclitaxel should be discontinued.

Neuropathy
Paclitaxel treatment should be discontinued in patients with neuropathy ≥ CTC grade 3.

Mucositis
For mucositis ≥ grade 3 chemotherapy should be delayed until mucositis is resolved to ≤ Grade 1 . Paclitaxel should be reduced from 175mg to 135mg/m^2 in subsequent cycles. If the

patient is already being treated at 135mg/m^2 then paclitaxel should be stopped. If mucositis persists at ≥ grade 3 for more than 2 weeks, or recurs, then discuss chemotherapy dose modifications with Chief Investigator. Mucositis should be treated symptomatically as per local standard practice

Febrile Neutropenia
Reduce carboplatin by AUC 1 and paclitaxel to 135mg/m^2 for next cycle and all subsequent cycles. If either carboplatin or paclitaxel have been dose reduced previously then treatment with drug should stop.

Grade 4 Thrombocytopenia
Reduce Cediranib dose to 15mg for all subsequent cycles.
Once a dose reduction has been made it should not be escalated. The patient should remain on the reduced dose.

Hypersenstivity
Paclitaxel:
If a hypersensitivity reaction occurs then patients may be retreated with paclitaxel. This will depend on the severity of the reaction and the specific reaction. Retreatment should be managed according to standard local practice

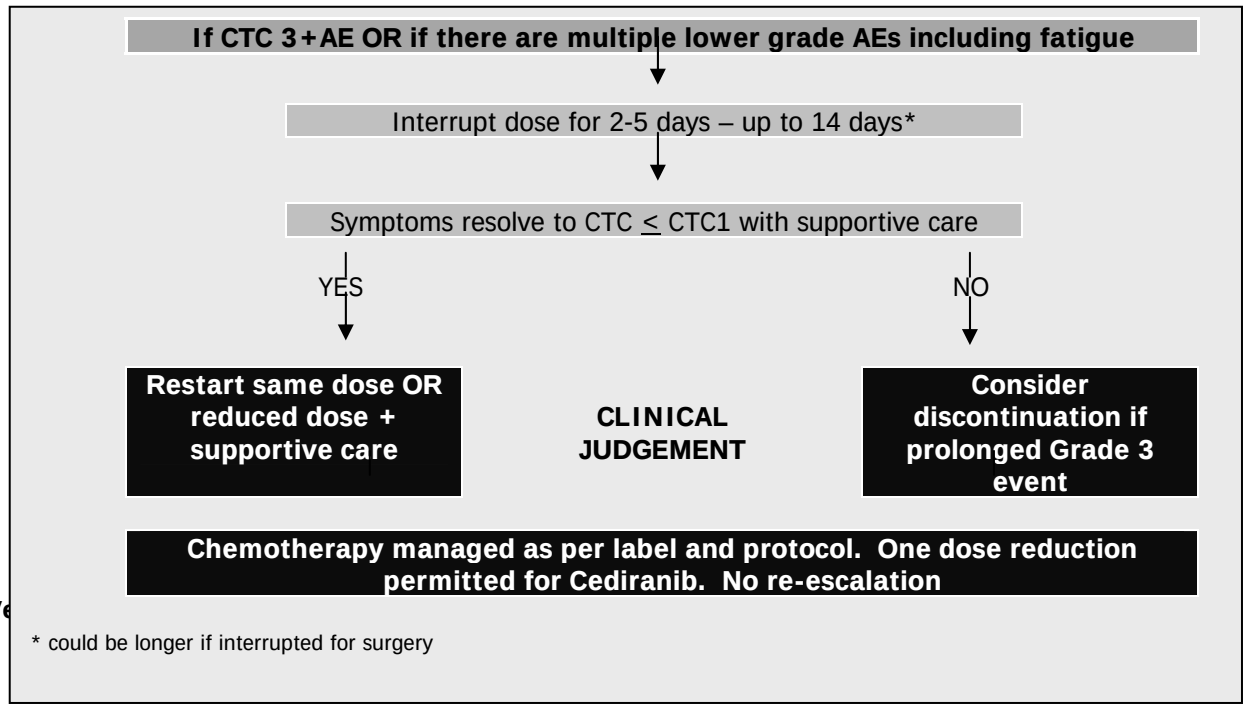
Carboplatin:
A hypersensitivity reaction to carboplatin should be managed according to standard local practice. Patients may be retreated according to standard local practice.

Cediranib Toxicities

General
With the exception of hypertension, short dose interruptions of cediranib study tablets are the first approach to the management of adverse events and dose reduction is also possible. For hypertension, early treatment with a calcium channel antagonist is recommended and in general dose interruptions and reductions should not be necessary.

Multiple low grade adverse events attributed to the blinded cediranib (e.g. diarrhoea, weight loss, dehydration and fatigue) can be treated by short dose interruptions (i.e. 2-5 days). Treatment can be restarted on resolution at the same dose.

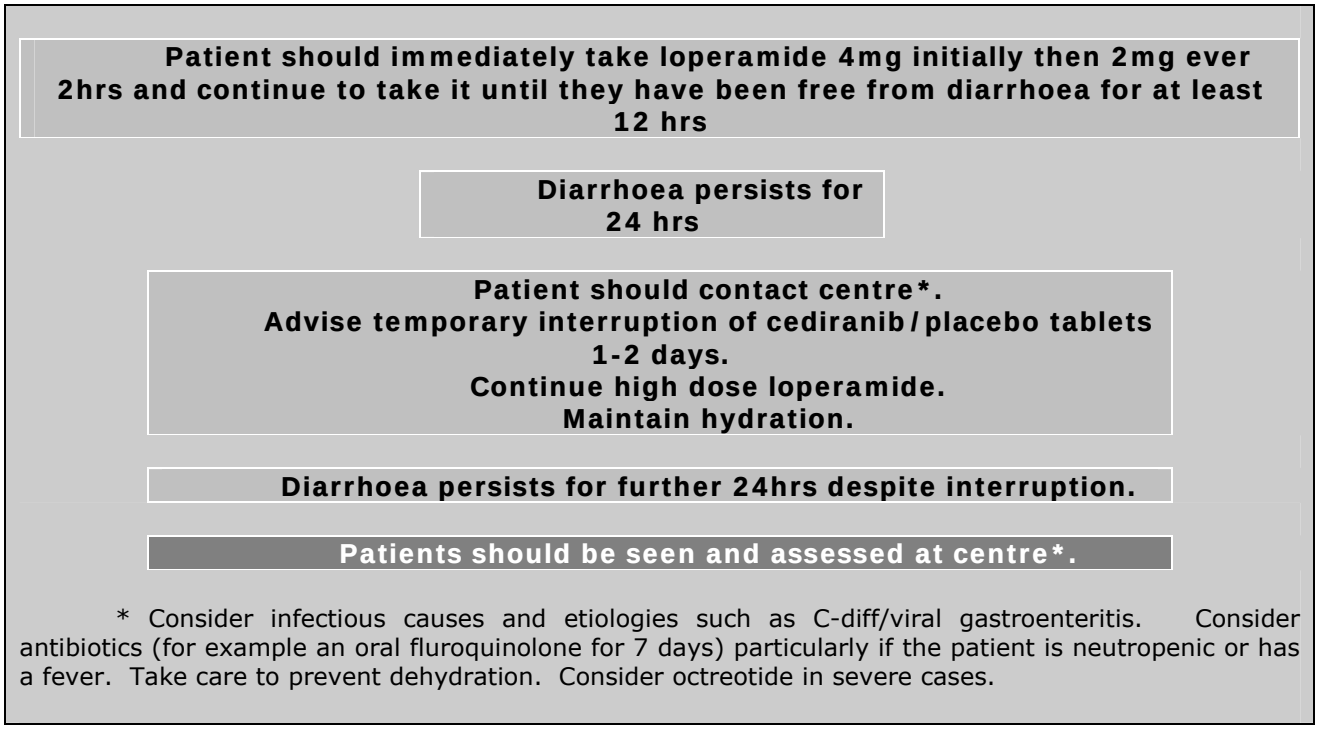
For CTC Grade 3 or above adverse events considered to be related to cediranib the blinded cediranib tablets should be withdrawn for up to 14 days. Once symptoms have resolved to CTC Grade 1 or less with supportive care the treatment can be restarted.



Thrombocytopenia
As noted above, any grade 4 toxicity while receiving cediranib or placebo (whether on chemotherapy of not) will result in a dose reduction from 20mg od to 15mg od for all subsequent cycles. Once a dose reduction has been made it should not be escalated. The patient should remain on the reduced dose.

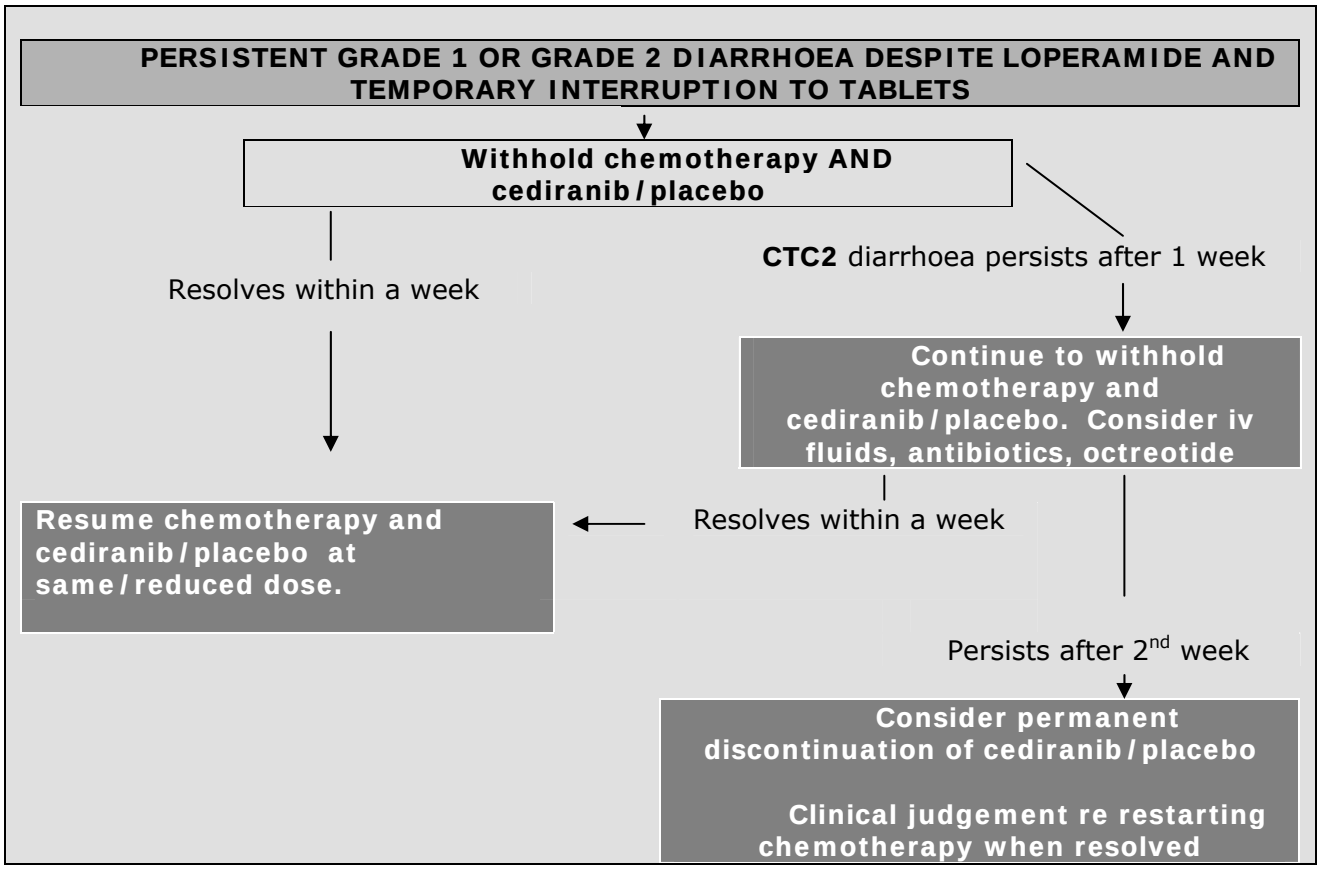
Diarrhoea
Cediranib is associated with diarrhoea and action should be taken to minimise its effects as soon as symptoms develop. Patients should be aware that they are likely to experience diarrhoea and should be given loperamide to take home with them. If diarrhoea occurs patients should immediately start loperamide after the first episode (4mg initially then 2mg every 2 hours) and continue to take it until they are free from diarrhoea for at least 12 hours. Patients should be encouraged to drink plenty of fluids. Patients should seek advice from either the treating consultant or study nurse if they have grade 1 or 2 diarrhoea persisting over 24 hours despite treatment with loperamide or grade 3 or above diarrhoea. Cediranib should be discontinued until recovery to baseline in cases of Grade 2 diarrhoea persisting for >24 hours despite treatment with loperamide or any case of grade 3 diarrhoea. Dose interruption and antibiotic therapy should be considered (particularly if neutropenic fever or diarrhoea is observed). If any grade of diarrhoea is associated with vomiting, marked abdominal distension or inability to take oral fluid, the patient should contact the treating hospital immediately. Within the differential diagnosis of diarrhoea other conditions should be considered, in particular neutropenia, C. difficile infection and other infective causes of diarrhoea and/or vomiting. If diarrhoea continues for >48hrs despite loperamide the patient should be seen by the study nurse or trial physician. The use of octreotide can be considered.

Cediranib Initial Management of Diarrhoea Figure



* Consider infectious causes and etiologies such as C-diff/viral gastroenteritis. Consider antibiotics (for example an oral fluroquinolone for 7 days) particularly if the patient is neutropenic or has a fever. Take care to prevent dehydration. Consider octreotide in severe cases.

Action to be taken for the blinded Cediranib tablets and chemotherapy if diarrhoea persists at the time of the next cycle of chemotherapy



Fatigue
Fatigue experienced by patients taking cediranib may be rapid in onset. Patients should contact the treating physician or study nurse if they develop grade 2 fatigue or more. Patients should be advised to take short treatment breaks from the blinded cediranib tablets for 2 to 3 days or longer up to a maximum of 14 days in order to relieve this symptom. Care should be taken to ensure the patient's nutrition and fluid intake is adequate. Other causes of fatigue should be considered including depression, hypothyroidism, anaemia, electrolyte imbalance and the effects of other drugs such as anxiolytics.

Hypertension (HT)
Increases in blood pressure are expected with anti VEGF inhibitors and can occur after the first dose. Blood pressure should be measured weekly during the first 4 weeks of treatment. Patients using anti-hypertensive medication before treatment are more likely to develop moderate to severe hypertension during cediranib treatment therefore blood pressure management must be optimised in these patients before starting treatment.

In all Cediranib studies, increases in blood pressure should be treated at an early stage in order to achieve and maintain control of blood pressure and to prevent complications. This is different to the standard therapy approaches normally associated with particular CTCAE grades of hypertension.

NCI CTCAE v.4 grade	Definition	Management
GRADE 1	Prehypertension (systolic BP 120-139mmHg or diastolic BP 80-89mm Hg)	**G1 – Consider increased BP monitoring**
GRADE 2	Stage 1 hypertension (systolic BP 140-159 mmHg or diastolic BP 90-99mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20mmHg (diastolic) or to >140/90 mmHg if previously within normal limits; monotherapy indicated	**G2 – Intervention is required on cediranib/placebo** **More than one agent may be required** if HT is not controlled
GRADE 3	Stage 2 hypertension (systolic BP>=160mmHG or diastolic BP>=100mmHG): medical intervention indicated: more than one drug or more intensive therapy that previously used indicated	**G3** – Proactive HT management plan requires more than one agent or dose increases of agents. **Assign G3 HT only if BP is not controlled after 48 hours of therapy (i.e. with two agents)**
GRADE 4	Life threatening consequences (e.g. hypertensive crisis)	**G4 - Stop Cediranib,** hospitilize with aggressive IV therapy as per hypertensive crisis management
GRADE 5	Death	

Triggers for starting anti-hypertensive therapy

Mild-Moderate HT

In normal medical practice, treatment may not be considered to be indicated but in Cediranib studies treatment is recommended if:

- Blood pressure is >140/90mmHg on 2 consecutive occasions more than 24 hours apart.
- CTC grade 2 Hypertension develops:
  - An increase in diastolic blood pressure of at least 20mmHg.
  - An increase in systolic blood pressure to 150mmHg or more.
  - An increase in diastolic blood pressure to 100mm Hg or more.

Recommendations for treatment of mild-moderate HT:

1. Continue cediranib/placebo at same dose and introduce treatment with a long-acting calcium channel antagonist (CCA) such as nifedipine, amlodipine, or felodipine (or other agent if CCA contra-indicated). CCAs appear to be the most effective agents to control Cediranib-induced HT, as they are vasodilators.
2. If BP still >140/90 and has not responded after 24 hours, increase dose of CCA
3. If BP still >140/90 and has not responded after a further 24 hours add in another anti-HT agent.
4. If 48 hours later BP remains uncontrolled or continues to increase, temporarily hold Cediranib tablets until BP $\leq$ 140/90.

5. Restart Cediranib (at same dose or with a dose reduction), when BP $\leq$140/90.
6. If BP remains uncontrolled or continues to increase despite dose reduction ad maximal anti-HT treatment, permanently stop Cediranib.

The long-acting calcium channel antagonist's listed above are examples of drugs to be used to treat mild to moderate hypertension. As these examples are not mandatory protocol treatment the products specified will not be considered non-investigational medicinal products (NIMPs).

Severe Hypertension
Severe hypertension is defined as an increase in diastolic blood pressure to at least 110mmHg or an increase in systolic blood pressure to at least 180mmHg on two readings at least 1 hour apart.

1. Temporarily hold Cediranib/Placebo and manage patient clinically (consider hospitalisation, iv therapy as necessary)
2. If BP controlled to $\leq$140/90 and where appropriate, restart Cediranib/Placebo at reduced dose level. Continue CCA anti-HT therapy and monitor BP closely (at least every 2 days until Cediranib steady state is reached at 7 days)
3. If BP increases after reintroducing Cediranib/Placebo, despite anti-HT therapy, consider if permanent discontinuation is indicated.

Proteinuria
If during the study, a patient has a change of two plus (++) from baseline on two consecutive urine protein dipstick measurements, or one three plus (+++) or greater measurement, please measure urine protein creatinine ratio or collect a 24 hour urine for total protein. A urine protein/creatinine ratio of 0.15 (urine protein and urine creatinine expressed in mg/dl) approximates a 24-hour urine protein of 105mg/24 hours or 0.15g/24 hours, which is the upper limit of normal (Rodby et al 1995, Schwab et al 1987, Wingo and Clapp 2000).If 24 hour proteinuria is classified as CTC grade 3 (4+ or 3.5g/24hours), cediranib/placebo should be discontinued until it falls to 1+ (up to 14 days; if continues beyond this, consider discontinuing cediranib/placebo). If nephrotic syndrome occurs, cediranib/placebo should be permanently discontinued.

Haemorrhage
Cediranib/placebo should be permanently discontinued in patients who have serious haemorrhage (i.e. haemorrhage requiring medical intervention).

Thyroid function
Cediranib/placebo has been associated with increases in TSH. In the majority of patients, this has not resulted in reductions in either total triiodothyronine (T3) or free thyroxine (T4) to below the lower limit of the normal range, but clinical hypothyroidism has been reported in a small number of patients. These patients have responded to replacement therapy without the need for stopping or reducing the dose of cediranib/placebo.

Replacement levothyroxine should be given when clinically indicated to normalise the thyroxine level to within the normal range, and before the patient becomes clinically symptomatic. Replacement levothyroxine therapy may also be considered in patients with TSH increases (and thyroxine levels within the normal range), together with AEs and symptoms suggestive of incipient hypothyroidism.

Reversible posterior leukoencephalopathy (RPLS)
Cases of MRI-documented RPLS have been reported in patients receiving cediranib in clinical studies. RPLS affects vascular endothelial cells in the brain that may lead to capillary leak and

oedema. It can present with non-specific symptoms such as headaches, seizures, lethargy, confusion, blindness and other visual and neurological disturbances. MRI is the most sensitive imaging modality to detect RPLS and is recommended in suspected cases to confirm the diagnosis.Cediranib/placebo should be immediately discontinued in all cases of RPLS. Additional measures to alleviate symptoms and control BP should also be undertaken.

5.7 Emergency Unblinding

Randomisation codes will be held within the drug management system.

Unblinding patient's Trial Drug is discouraged during the trial as blinding is critical to is integrity. Emergency unblinding may take place in situations where the safe management of the patient's medical condition **necessitates knowledge of the study medication by the person(s) responsible for the patients care**. The blind for that subject may be broken by the treating physician or responsible pharmacist.

The trial allocation will only be revealed to individuals on a "need to know" basis and should never be revealed to the Study Statistician (apart from after the final study analysis).

Where unblinding is being considered, during working hours the case **MUST** first be discussed with the Chief Investigator. Out of hours, in an emergency situation this is not necessary but before breaking the blind of an individual subject's blinded treatment, the Investigator should have determined that the information is necessary, i.e. that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding. For any treatment code unblinding, the reason for decision to unblind and parties involved must be documented in the patient's medical record and documented on the patient's Case Report Forms. Treatment identification information should be kept confidential and should be disseminated only to those individuals that must be informed for medical management of the patient.

The CR-UK Clinical Trials Unit will be notified of all emergency unblindings via the Cenduit system. A log documenting all emergency unblinding throughout the duration of the trial will be maintained at the Clinical Trials Unit.

All principal investigators and site pharmacists will have access via the Cenduit system that allows them to break the blind for an individual patient in an emergency situation as described above.

Site personnel will access the Cenduit system via a secure website, using individual access codes. Full telephone support is available via a toll free telephone number. Study specific user guides and PIN details will be sent to each site after initiation.

The toll free access line for the Cenduit helpdesk is 00 800 1012 1960.

5.8 Unblinding Following Final Analysis

Routine unblinding will take place after the final statistical report has been completed.

Any patients who remain on study treatment (cediranib[AZD2171] or placebo) at this time will be notified of the treatment arm they have been randomised to.

<u>Patients Remaining on the Active Treatment Arm</u>
<u>If the active treatment arm (cediranib) looks to give an advantage over the current routine treatment, then patients who are currently receiving the active treatment will be given the opportunity to remain on this if they wish.</u>

If the active treatment arm does not look to give an advantage over the current routine treatment, then treatment will be discontinued as soon as possible, unless there are exceptional cases of ongoing clinical benefit which, in the opinion of the investigator, are attributable to cediranib.

Patients Remaining on the Placebo Arm
Placebo treatment will be discontinued as soon as possible for any patients remaining on placebo treatment. There is no plan to offer cross over to active treatment for these patients.
At the point of unblinding, full instruction on the process will be given to the sites by the study Trial Management Group (TMG). The TMG will be responsible for making a judgement on whether the active treatment is considered to give an advantage over the current routine treatment. This decision will be made after full review of the final statistical report

6 PHARMACOVIGILANCE

Safety assessments will be performed in line with guidance specified in The Medicines for Human Use (Clinical Trials) Regulations 2004.

6.1 Adverse Event (AE)

6.1.1 Definition of an Adverse Event (AE)

An adverse event is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

6.1.2 AE Reporting

Adverse events must be recorded as they are reported, whether spontaneously volunteered or in response to questioning about well being at trial visits. The questioning about adverse events will cover the current visit as well as the period of time between the previous and the current visit. All adverse events must be documented in the patient's medical records.

All adverse events must be followed until resolution, or for at least 30 days after discontinuation of study medication, whichever comes first or until toxicity has resolved to baseline or $\leq$ Grade 1, or until the toxicity is considered to be irreversible. Perceived lack of efficacy is not an adverse event.

An exacerbation of a pre-existing condition is an adverse event.

All adverse events and toxicities must be graded according to the NCI Common Terminology Criteria for adverse events (NCI-CTCAE) Version 4.0
(http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf.)

6.2 Serious Adverse Event (SAE)

6.2.1 Definition of a SAE

A serious adverse event (SAE) is defined as any of the following, whether or not considered related to the trial treatment.

- Results in Death
- Life-threatening (i.e. at the time of the event)*
- Requires inpatient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is considered medically significant by the Investigator***

*Life threatening means that the patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.

**Requires in-patient hospitalisation should be defined as a hospital admission required for treatment of an adverse event.

***Considered medically significant by the Investigator are events that may not result in death, are not life threatening, or do not require hospitalisation, but may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

6.2.2 Reporting of a SAE

For guidance on completing the initial and follow up SAE forms please refer to the SAE Form Completion Guidelines, which will be provided by the Pharmacovigilance Office, CR-UK CTU, Glasgow.

If a Serious Adverse Event occurs that requires reporting, a Serious Adverse Event reporting form should be completed and faxed within 24 hours of becoming aware of the event to:

Pharmacovigilance Office, CR-UK CTU, Glasgow
Fax no: +44 (0) 141 301 7213
Tel no: +44 (0) 141 301 7209/7211

The Chief Investigator will receive notification of all SAEs shortly after they are received by Pharmacovigilance and confirm agreement with the causality assessment made by the reporting Investigator.

SAEs must be reported locally by the PI at each site in accordance with the local practice at their site (i.e. Ethics Committee, R&D Office).

A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available. If the SAE is a suspected SUSAR then follow up information must be provided as requested by the CR-UK Clinical Trials Unit and Chief Investigator.

SAEs are required to be reported from randomisation for up to 30 days after last administration of study treatment. Any SAE that occurs after 30 days post treatment (with no time limit) is also required to be reported if the Investigator thinks that the SAE is related to protocol treatment (is a SAR), or is medically important. Post treatment SARs should be reported by contacting the CR-UK Clinical Trials Unit, Glasgow:

Email: l.connery@clinmed.gla.ac.uk
Tel: +44(0) 141 301 7209
Fax: +44(0) 141 301 7213

6.2.3 Definition of a Serious Adverse Reaction (SAR)

A serious adverse reaction (SAR) is an SAE that may be related to trial treatment. The assessment of "relatedness" is primarily the responsibility of the Principal Investigator at site or agreed designee. SAEs that will be considered related will include any SAE that is documented as possibly, probably or definitely related to protocol treatment. The assessment of relatedness is made using the following:

Relationship	Description
Unrelated	There is no evidence of any causal relationship.

Possible	There is some evidence to suggest a causal relationship (e, g. the event occurs within a reasonable time after administration of the trial medication). However the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors in unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

6.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

6.3.1 Definition of a SUSAR

A SUSAR is any suspected serious adverse reaction that is unexpected. Unexpected is any reaction that is not a known reaction listed in the Investigator Brochure or Summary of Product Characteristics of the trial treatments.

6.3.2 Procedure for Identifying a SUSAR

The CR-UK Clinical Trials Unit will prepare a SUSAR checklist for identifying potential SUSARS. The checklist is a list of the known expected reactions to carboplatin, paclitaxel or Cediranib against which a SAR can be checked. For any SARs not listed on the checklist the Chief Investigator will be contacted for an opinion of SUSAR status. The Chief Investigator (or designee) is responsible for deciding if a SAR is a SUSAR.

Below is a list of known expected reactions to cediranib:

Expected Reactions	Description
Events due to Cediranib	Hospitalisation due to: • Diarrhoea • Fatigue • Hypertension • Hand and foot syndrome • Nausea • Vomiting • Dehydration • Hoarseness (dysphonia) • Muscle Weakness • Proteinuria • Dry mouth & oral mucosal inflammation • Reversible posterior leukoencephalopathy syndrome (RPLS) • Increase in transaminases • Thrombocytopenia

6.3.3 Reporting of a SUSAR

The CR-UK Clinical Trials Unit is responsible for the expedited reporting of all SUSARS to the MHRA, and any other appropriate regulatory authorities, Main Research Ethics Committee, PI at trial sites, the trial Sponsor and AstraZeneca:

- Fatal or life threatening SUSARS will be reported within 7 days of the Trials Unit receiving the initial report. Any additional information will be reported within eight days of sending the first report.

- All other SUSARS will be reported within 15 days of the Trials Unit receiving the initial report.

6.4 Annual Safety Reports

Annual safety reports will be prepared and submitted by the CR-UK Clinical Trials Unit Glasgow for all SAEs and SUSARS reported for the trial. Annual Safety Reports will be submitted to the MHRA, lead ethics committee, and trial Sponsor on the anniversary of obtaining the Clinical Trial Authorisation.

6.5 Non Investigational Medicinal Products (NIMPs)

NIMPs are "Products which are not IMPs" and are referred to in Art. 2(d) of Directive 2001/20/EC and may be supplied to patients participating in a trial and used in accordance with the protocol. For instance, some clinical trial protocols require the use of medicinal products such as concomitant or rescue/escape medication for preventive, diagnostic or therapeutic reasons and/or ensure that ensure adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response. These medicinal products do not fall within the definition of investigational medicinal products in Directive 200/20/EC and can be referred to as "non-investigational medicinal products" (NIMPs)."

Any SAE that could be the result of administration of a NIMP must be reported as a SAE. This can be an SAE related to the NIMP or a reaction between an IMP and NIMP.

The NIMP/s identified for this trial are <u>Carboplatin, Paclitaxel and Loperamide.</u>

7 ASSESSMENT AND FOLLOW-UP

Toxicity will be assessed every 3 weeks whilst the patient is having chemotherapy. Patients will be evaluated for response every 6 weeks during chemotherapy. MRI or CT scans will be carried out after every 2 cycles of chemotherapy (6 weekly intervals). Following the end of chemotherapy patients will be seen not less than at 2 monthly intervals and will have CT or MRI scans every 2 months during the 1st year of follow-up until disease progression confirmed.

Quality of life will be measured using the EORTC QLQ-C30 and QLQ-CX24 cervix subscales. This will be collected prior to each cycle and at each follow-up visit until progression or for a maximum of 1 year.

7.1 Monitoring for Toxicity, Efficacy and Quality of Life

All chemotherapeutic regimens given to cervix cancer patients following radiotherapy can be myelosuppressive. For this reason patients will have weekly blood counts during the first cycle of chemotherapy. If the count has not returned to normal, carboplatin and paclitaxel dosage will be modified as listed in paragraph 5.3 (dose modifications for toxicity). Neutropenia by itself is not an indication for dose reduction. However doses should be reduced following febrile neutropenia. It is not expected that Cediranib would increase the incidence of neutropenia but this drug may contribute to thrombocytopenia. Cediranib/placebo dosage should be reduced if Grade 4 thrombocytopenia is seen.

Investigations during and after treatment
After Cycle 1

Between D2 and D7	For patients with a previous history of hypertension it is requested the patients GP checks the patients blood pressure during the 1st week of treatment at some point between D2 and D7.
Day 8, Cycle 1	Full blood count including WBC, neutrophils and platelets,

	Biochemistry (U+Es, LFTs, Ca) Plasma sample for VEGFR2 levels* Vital signs including blood pressure monitoring Toxicity assessment
Day 15, Cycle 1	Full blood count including WBC,neutrophils and platelets, Biochemistry (U+Es, LFTs, Ca) Plasma sample for VEGFR2 levels* Vital signs including blood pressure monitoring Toxicity assessment
Day 1, Cycle 2	Full blood count including WBC, neutrophils and platelets Biochemistry (U+Es, LFTs, Ca) Plasma sample for VEGFR2 levels* Urinalysis Vital signs including blood pressure monitoring Clinical examination Evaluation ECOG performance status Toxicity assessment
Day 8, Cycle 2	Plasma sample for VEGFR2 levels*
Day 1, Cycle 3	Full blood count including WBC, neutrophils and platelets, Biochemistry(U+Es, LFTS, Ca), thyroid function tests (TFTs) Plasma sample for VEGFR2 levels* Urinalysis Vital signs including blood pressure monitoring Evaluation ECOG performance status, Toxicity assessment Clinical Examination (Pelvic examination if appropriate) CT scan of chest abdomen and MRI scan of pelvis if appropriate 1 week before cycle 3 chemotherapy to assess response
Day 1, Cycle 4	Full blood count including WBC, neutrophils and platelets Biochemistry (U+Es, LFTs, Ca) Plasma sample for VEGFR2 levels* Urinalysis Vital signs including blood pressure monitoring Evaluation ECOG performance status Toxicity assessment Clinical examination
Day 1, Cycle 5	Full blood count including WBC, neutrohils and platelets, Biochemistry(U+Es, LFTS, Ca), thyroid function tests (TFTs) Plasma sample for VEGFR2 levels* Urinalysis Vital signs including blood pressure monitoring Evaluation of ECOG performance status Toxicity assessment Clinical Examination (Pelvic examination if appropriate) CT scan of chest abdomen and MRI scan of pelvis if appropriate 1 week before cycle 5 chemotherapy to assess response
Day 1, Cycle 6	Full blood count including WBC, neutrophils and platelets Biochemistry (U+Es, LFTs, Ca), Plasma sample for VEGFR2 levels* Urinalysis Vital signs including blood pressure monitoring

	Evaluation ECOG performance status Toxicity assessment Clinical examination
1st Follow-up	CT scan and/or MRI 1 week before follow-up visit Clinical examination including pelvic examination Toxicity assessment Full blood count including WBC, neutrophils and platelets Urinalysis Biochemistry (U+Es, LFTs, Ca) Plasma sample for VEGFR2 levels* Vital signs including blood pressure monitoring Evaluation ECOG performance status Toxicity assessment
Further follow-up	Follow-up until tumour progression or toxicity brings about cessation of study treatment CT scan of chest, abdomen and pelvis or MRI scan to be performed at 2 monthly intervals in 1st year of follow up until disease progression confirmed. Thereafter only required in subsequent years of follow-up if patient has not had disease progression, only as clinically indicated i.e. disease progression suspected. Clinical follow-up at 2 monthly intervals with FBC, Biochemistry, yital signs including blood pressure monitoring, urinalysis, evaluation ECOG performance status, toxicity assessment and clinical examination at each visit. Thyroid function tests 2-monthly while on follow-up. Plasma sample for VEGFR2 levels at follow-up month 4 and month 6*. **** Plasma blood samples for VEGFR levels. Translational aspect of trial, only to be collected for patients who have consented to this. Please refer to appendice VII for further details for collection of blood samples.*** Prior to progression, patients should be followed up 2 monthly until end of year 3, every 6 months during years 4 and 5 and yearly thereafter. After disease progression is documented, patients should be followed up 6 monthly during the first 5 years of randomisation and yearly thereafter.

7.2 Quality of Life Assessment

Completion of QoL forms (QLQ-30 and QLQ-CX24 see Appendix V) should occur before medical assessments are performed, or chemotherapy administered. The first form that is required is at screening, after consent to participate has been given and prior to randomisation, as a baseline measurement. The QoL form should be completed at the onset of every cycle of chemotherapy, end of treatment and then every 2 months during first year of follow-up.

8 TRANSLATIONAL RESEARCH - PLASMA SAMPLES

8.1 Rationale

Cediranib has not been studied in cervical carcinoma. Therefore, the primary objective is to provide proof-of-principle for cediranib inhibiting VEGF signalling in carcinoma of the cervix. Evaluation of the VEGFR signalling inhibitor cediranib in patients with recurrent carcinoma of the cervix will be supported by the identification of suitable markers of biologic activity. The secondary objective is, therefore, to identify biomarkers that predict cediranib response.

8.2 Samples

- Serial plasma samples from centres with facilities for plasma separation: two pre-treatment, during treatment cycles 1 – 6 (prior to dosing), cycle 2 day 8, at routine follow up visits (months 2, 4 and 6) Samples should be collected weekly during the first cycle and every 3 weeks thereafter.
- Store buffy layer from a pre-treatment sample for future genotyping

The translational research aspect of the trial is optional to patients, and samples should only be collected for patients who have consented to this. Please refer to appendice VII for further details for collection of blood samples.

9 TRANSLATIONAL RESEARCH - MRI SCAN SUB STUDY

Funding has been granted from Cancer Research UK for an MRI Scan sub study which will take place in a small number of centres (approx 7 centres) involving 30 patients entered to the main study who have consented to participate in the sub study. Patients entered to the substudy will require to have localised disease in the pelvis. A separate Patient Information Sheet/Consent Form will be used for the substudy.

Summary of substudy:
30 patients from this study will undergo 3 additional DCE-MRI scans with Diffusion weighted imaging (two baseline scans and day 8) which will be used to assess response to chemotherapy +/- cediranib as changes in blood flow in tumour and normal tissue may predict early response or toxicity, particularly development of fistulae or bowel perforation. This study will be a pilot to establish the standardisation of methodology of the NCRI cervix subgroup and the feasibility of imaging across centres.

Centres participating in this sub-study should refer to appendix VIII of the protocol which has MRI protocol which has to be followed.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample Size

The required sample size is 80 patients, 40 per arm, in order to observe 69 progressions or deaths. The study is designed using the methodology of Rubinstein et al[23]. This study is designed to detect a 50% improvement in median progression free survival with cediranib from 4 months to 6 months with a 80% power, 20% 1-sided level of statistical significance. This sample size also provides 85% power at the 10% 1-sided level of statistical significance to detect a 75% increase in median progression-free survival from 4 months to 7 months.

A result favouring cediranib that is statistically significant at the one-sided 20% level, but not at the 1-sided 10% level, will require other supportive data in terms of a statistically significant difference in the reduction in sVEGFR-2 levels from baseline to day 28 between the groups (increased reduction with cediranib) before a subsequent phase III would be considered.

Data from Batchelor T et al Cancer Cell 2007 indicates that the standard deviation in the change in sVEGFR-2 (log 10) levels from baseline is 0.27 and the expected change is 0.19. Assuming no change in the placebo arm, to detect this difference between the arms requires 54 patients (90% power, 10% 1-sided level of stat sig). Allowing for 10% being unevaluable (10% will have progressed/died before day 28) the study will recruit 60 patients in which this PD end-point will be measured.

10.2 Analytical Plan

10.2.1 Primary efficacy analysis

The primary analysis of the progression-free survival end-point will be based on the intention-to-treat (ITT) population. Progression-free survival is defined as the time from randomisation to confirmed progression or death from any cause (whichever occurs first).

The primary analysis will be conducted using Cox regression via a model incorporating study arm and the factors used in the minimisation algorithm (see section 4.5). The p-value associated with study arm will be obtained from this model. A test for interaction will be conducted to assess whether the effect of study arm depends on the other clinical factors used in the minimisation algorithm. This analysis will be conducted at the end of the minimum follow-up period once the required number of events (69) for progression-free survival have been observed.

The estimated hazard ratio derived from the Cox regression model will be given together with the associated 80% confidence interval.

A Kaplan-Meier curve will be used to illustrate the relative progression-free survival experience on the two treatment arms.

10.2.2 Secondary efficacy analysis

Changes in sVEGFR-2 (log 10) from baseline to day 28 will be compared between the treatment arms using a t-test.

Overall survival (defined as the time from the date of randomisation until death from any cause) will be analysed of using the same approach as that for progression-free survival.

Response rates (Complete and Partial combined) will be compared between the arms using logistic regression via a model incorporating study arm and the factors used in the minimization algorithm. The p-value associated with study arm will be obtained from this model. An 80% confidence interval for the odds ratio will be provided.

10.2.3 Safety analysis

The worst recorded toxicity grade for each patient on the NCI-CTCAE toxicity scale (version 4.0) will be summarised by treatment arm and compared using the Mann-Whitney U-test.

10.2.4 Quality of life analysis

The analysis of quality of life data will be based in AUC techniques [25].

11 REGULATORY ISSUES

11.1 Clinical Trials Authorisation (CTA)

Cancer Research UK Clinical Trials Unit, Glasgow will apply to the MHRA for a clinical trials authorisation (CTA) to conduct the trial and will also be responsible for the maintenance of the CTA.

11.2 Ethics and Research & Development Approval

Ethics favourable opinion will be sought for the study from a Main REC prior to commencement of this trial. Further to that approval each participating site will be responsible for obtaining

their own local approval by submitting an SSI to their appropriate R&D department for management approval.

Participating sites will not be activated to recruitment until both management approval has been obtained, and a signed clinical trial agreement between the local R&D office and the study sponsor has been executed.

The study will be carried out in accordance with the principles of ICH GCP and the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo 1978, Venice 1983, Hong Kong 1989, South Africa 1996, Edinburgh 2000 and Seoul 2008).

11.3 Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, the participant has been given an information sheet and a minimum of 24 hours to consider trial participation. Signed participant consent must be obtained, the consent forms should also be signed by the person undertaking the consent procedure at site, who must be detailed on the Staff Contact and Responsibility Log as having this authorisation. The Principal Investigator is responsible for ensuring if taking consent is delegated to a designee, the designee is suitably qualified by training or experience to take informed consent.

The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the best interests of the participant, but the reasons for doing so must be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

An original completed consent form must be retained at each site in the appropriate section of the Investigator Site File, and a photocopy placed in the patient's medical records. All patients must be given an original of the signed patient information sheet and consent form for their records. A Consent Notification Form must be submitted with the randomisation form. Consent forms must be retained on site and not submitted to the Trials Office.

In the event that new patient information sheets/consent forms are produced throughout the duration of the study, it maybe that patients already participating in the study should be re-consented to the updated version of the patient information sheet. However, if the principal investigator decides that this is not in the best interests of the patient re-consent is not required. Decisions to not re-consent patients must be documented in the patient's medical records.

11.4 Confidentiality

National Health Service Guidelines for storage, transmittal and disclosure of patient information will be followed at all times. Data on patients treated in the course of the study will be documented anonymously, that is patients will be identified only by a patient number and initials.

This study will be carried out to GCP Guidelines. Following formal admission to the study, patient data will be recorded in the hospital case records in the usual way including the circumstances of their entry into the study. Additionally data will be held in hard copy study case report form (CRF). These files will be identified by a study number, date of birth and patient initials only.

Representatives from the Study Sponsors and from the Regulatory Authorities will be given access to the records that relate to the study. They will have full access to all trial data as required.

Results of the study may be communicated at scientific meetings and will contribute to the scientific literature. At no time will this be done in such a way that an individual patient may be identified.

11.5 Liability, Indemnity and Insurance

The Hospital Trust/Health Board at each participating site is responsible for the following:

1. Acts and omissions of its own staff and others engaged by it, including the Clinical Trials Unit and PI;
2. Ensuring the appropriate insurance administered by the National Health Service Litigation Authority is in place;
3. Ensuring any non-NHS employees involved in the clinical trial have Honorary Contracts with the Trust to cover access to patients and liability arrangements.

These responsibilities are outlined and agreed within the Clinical Study Agreement.

No special insurance is in place for patients in this study other than standard NHS liability insurance providing indemnity against clinical negligence. This does not provide cover for non-negligence e.g. harm caused by an unexpected side effect of participating in a study.

11.6 Sponsor

This trial is co-sponsored, the co-sponsors are NHS Greater Glasgow and Clyde and University of Glasgow, responsibilities will be assigned to the CRUK CTU and NHS Trusts taking part in this study. Details of responsibilities will be outlined in the clinical trial agreement that should be signed prior to site initiation.

11.7 Funding

This study is being funded by a grant from Cancer Research UK (CTAAC), and also by an educational grant from Astra Zeneca under the terms of their collaboration with the National Cancer Research Network.

11.8 Monitoring

Central Monitoring

Study sites will be monitored centrally by checking incoming forms for compliance with the protocol, data consistency, missing data and timing. Study staff will be in regular contact with site personnel (by phone/fax/email/letter) to check on progress and deal with any queries that they may have.

On-Site Monitoring

All participating study sites will be visited by a member of the CR-UK CTU monitoring team. The PI will allow the study staff access to source documents as requested. In addition, the pharmacy department responsible for the trial will be visited to allow monitoring of the pharmacy site file and review of security, storage and accountability of trial drugs. Investigators and site staff will be notified in advance about forthcoming monitoring visits. On occasion, members of the CR-UK CTU monitoring team may be accompanied by other trial staff from the unit for training purposes.

11.9 Audits and Inspections

Trial Investigators must permit trial related monitoring, audits, REC review and regulatory inspections as required, by providing direct access to source data, CRFs and other documents (patients medical records, trial site file, and other pertinent data).

The study may be subject to inspection and audit by NHS Greater Glasgow and Clyde under their remit as Sponsor, the CRUK CTU and other regulatory bodies, i.e. the MHRA, to ensure adherence to GCP. If an inspection is scheduled at any participating site, the site must notify the CR-UK CTU at the earliest opportunity.

12 ALLOCATION OF STUDY RESPONSIBILITIES

The co-sponsors of this clinical trial are NHS Greater Glasgow and Clyde and University of Glasgow.

Prior to study initiation, a non-commercially funded clinical trial co-sponsorship agreement will be put in place between NHS Greater Glasgow and Clyde and University of Glasgow. The role and liabilities each organisation will take are laid out in the agreement signed by both organisations. The University of Glasgow shall be responsible for carrying out the obligations and responsibilities set out in the aforementioned agreement, and shall be deemed the "sponsor" for the purposes of Part 3 of the Regulations in relation to the Study. NHS Greater Glasgow and Clyde shall be responsible for carrying out the obligations and responsibilities set out in the agreement, and shall be deemed the "sponsor" for the purposes of Parts 4, 5, 6 and 7 of the Regulations in relation to the Study.

A Clinical Study Agreement will be put in place between NHS Greater Glasgow and Clyde (legal name Greater Glasgow Health Board) and each of the participating sites. This agreement outlines the responsibilities of each party's responsibilities in the running of the trial as well as the Chief Investigator (CI), the Cancer Research UK Clinical Trials Unit, Glasgow (CTU), and the Principal Investigator (PI) at the Participating Site.

12.1 Co-Sponsor Responsibilities (GG&CHB/University of Glasgow)

The Sponsor's responsibilities will be for Authorisation and Ethics Committee opinion, GCP and Conduct, and Pharmacovigilance. The majority of the Sponsor's responsibilities have been delegated to the Chief Investigator (CI) who performs these via the CTU as the co-ordinating centre for the study. As such, the main role of the Sponsor is to ensure that the CI and CTU fulfil their responsibilities as outlined in the Clinical Trial Agreement and to ensure that any identified "risks" either have controls or action points put in place.

12.2 Chief Investigator (CI)

The CI has delegated the majority of his/her responsibilities to the CTU. The CI is directly responsible for ensuring the protocol and any amendments are in place, for review of SAEs and determination if SAEs meet the criteria for a SUSAR. The CI is also responsible for providing advice and recommendations on medical issues that arise involving the management of the patients on the study.

12.3 CR-UK Clinical Trials Unit (CTU)

The CTU are responsible for the overall management of the clinical trial. This includes all regulatory submissions (ethics, R&D and CTA) and any amendments, all administration relating to the submissions and any amendments, circulation of all correspondence to participating sites, data management, monitoring of data quality and safety, ongoing communication with participating sites, management of SAE/SUSAR reporting, and where applicable the management of any financial arrangements.

12.4 Participating Site

The Participating Site is responsible for the management of the trial within their site. This includes ensuring local ethical and management approval has been given, ensuring the study is conducted according to ICH GCP requirements, and ensuring the appropriate insurance or indemnity is in place. The Participating Site is also responsible for arranging access for on-site monitoring and auditing as identified in the study protocol and also for regulatory inspections.

12.5 Principal Investigator (PI)

The PI is responsible for the delegation of study activities within their site and ensuring all personnel are adequately trained and qualified to carry out their responsibilities. The PI will be required to provide evidence of GCP training (usually a certificate) or undergo the required GCP training. Regarding the management of patients within their site, the PI is responsible for the safety and well being of trial patients, reporting any deviations from the protocol to the coordinating trial office as well as any SAEs or safety issues. Full details of the responsibilities of the PI are outlined in the Clinical Trial Agreement. Two original copies of this will be held – one with the Sponsor and the other at the participating site. A photocopy of the signed agreement will also be held at the coordinating trial office.

13 TRIAL MANAGEMENT AND DATA COLLECTION

13.1 Study Start Up

Sites wishing to participate in the study should contact the Cancer Research UK Clinical Trials Unit, Glasgow to obtain trial information and start up packs (containing core documents and regulatory submission information/documents).

A PI must lead the study at each site, he/she will be responsible for providing the CR-UK CTU will all core documentation. A site initiation will be done via a telephone call between the CR-UK Clinical Trials Unit and the appropriate site staff or via accessing the on-line initiation slides. The site will be notified by email or fax when they are activated and are able to recruit patients to the trial.

13.2 Core Documents

These documents consist of:

- Clinical Study Agreement
- Site Contact Details
- Staff Contact and Responsibilities log
- Confirmation of favourable Site Specific Assessment (SSA)/ Trust R&D Approval letter
- Local versions of Patient Information Sheets, Consent Forms and GP Letters on hospital headed paper.
- Biochemistry and Haematology normal ranges and laboratory accreditation certificates
- Up to date, signed and dated CV's for the Principal Investigator, Co-Investigators and Lead Pharmacist must be provided. The CV should detail the qualifications, experience and training (including GCP training) of site personnel relevant to their role in the study, and should be updated every 2 years.

If circumstances change at the site (i.e. change of PI, hospital address etc) new documents must be completed and sent with a cover letter to the CR-UK Clinical Trials Unit, Glasgow.

13.3 Data Collection

Case Report Forms (CRFs) will be supplied electronically to sites by the coordinating trial office. These forms must be completed in accordance to the CRF completion guidelines issued with the CRFs.

Entries to the CRFs will be made in black ballpoint pen and must be legible. Any errors must be crossed out with a single stroke, the correction inserted and the change initialled and dated by the Investigator or the appropriate site personnel with this delegated responsibility as noted on the Staff Contact and Responsibilities Sheet. Correction fluid must not be used.

Please ensure that all data submitted on CRFs are verifiable in the source documentation or that any discrepancies are recorded and explained.

If a patient withdraws from the study during the treatment phase, the reason must be noted on the Treatment Completion/Withdrawal Form and in the patient's medical record, the patient must be followed-up as per protocol. If the patient withdraws their consent to any further participation in the study (treatment and follow-up) a Consent Withdrawal Form must be completed and no follow-up is required again this must be documented in the patient's medical record.

Completed CRF pages should be sent to:

CIRCCa Study Clinical Trial Co-ordinator
Cancer Research UK Clinical Trials Unit
Level 0
Beatson West of Scotland Cancer Centre
1053 Great Western Road
GLASGOW
G12 0YN

Trial sites should keep a copy of all completed CRFs.

All the CRFs must be returned for data entry and ultimately, statistical analysis.

CRFs from the study will be stored in line with current regulatory requirements. Other essential documents, including source data, consent forms, and regulatory documentation, will be archived by the Investigator, in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection as required.

13.4 Follow-up

Prior to progression, patients should be followed up 2 monthly until end of year 3, every 6 months during years 4 and 5 and yearly thereafter. After disease progression is documented, patients should be followed up 6 monthly during the first 5 years of randomisation and yearly thereafter.

13.5 Trial Management Group (TMG)

A TMG will oversee the running of the trial. Members of the TMG will include the Chief Investigator, Co-Investigators, Project Manager, Clinical Trial Co-ordinator, Trial Statistician, IT Staff, Quality Assurance Manager and Clinical Trial Monitor.

The TMG will meet every 2 months or as required, meetings may be by teleconference.

13.6 Trial Steering Committee (TSC)

A TSC will provide overall supervision for the trial. The TSC will be responsible for monitoring the progress of the trial towards its interim and overall objectives, focusing on adherence to the protocol, Good Clinical Practice (GCP), and patient safety. The TSC will include independent members who are not directly involved in other aspects of the trial.

13.7 Data Monitoring and Ethics Committee (DMEC)

A DMEC will be established for the trial. The DMEC will assess at intervals (planned or on request) the progress of the trial, the safety data, the critical efficacy endpoints, and will make any recommendations to the Sponsor and TMG whether to continue, modify or stop the trial.

14 QUALITY ASSURANCE

Quality Assurance/Quality Control will be maintained by the following requirements and activities:

At Site

- All study sites taking part in the trial will be required to participate in site initiation to ensure compliance with the protocol and allow training on study procedures and data collection methods. This will be done via a telephone call between the CR-UK Clinical Trials Unit and the appropriate site staff or via accessing the on-line initiation slides.
- Trial Investigators and site staff must ensure that the trial is conducted in compliance with the protocol, GCP and the applicable regulatory requirements.
- The CTU will assist the Trial Investigators and check they are complying with the protocol, GCP and regulatory requirements by monitoring trial documentation. Trial data and documentation will be checked for completeness, accuracy and reliability at monitoring visits. All participating study sites will be visited by a member of the CTU monitoring team. Investigators and sites will be notified in advance about forthcoming monitoring visits.

Centrally

- Central monitoring of trial data will be performed by the Trial Statistician and Clinical Trial Co-ordinators by checking incoming forms for compliance with the protocol, data consistency, missing data and timing.
- The CTU will control data consistency and data quality by entering trial data onto the CTU trial database. Computerised and manual consistency checks will be performed and queries issued in cases of inconsistency or missing information. A full audit trail of any changes to the database will be maintained.
- An independent DMEC will be established to oversee the safety and interim efficacy of the trial and will report their findings and recommendations to the TSC and TMG for implementation. The complete DMEC reports will remain confidential to the DMEC members and the trial statistician.
- The TSC will ensure the trial is being managed effectively by the TMG.
- The TMG will ensure the trial is being managed according to the protocol, GCP and regulatory requirements on time and within budget.
- Non-compliance with the protocol will be discussed with the TMG and trial Sponsor. Major deviations from the protocol or significant breaches of GCP may require recruitment to be suspended temporarily at the site while an investigation of the non-compliance is conducted. The outcome of such investigations will be discussed with the trial sponsor who will decide the appropriate course of action. The trial sponsor will decide if recruitment can resume or if the trial requires to be terminated at the site under investigation. If there is evidence of a serious breach of GCP, the trial Sponsor may decide it is necessary to report the breach to the regulatory authorities.

15 END OF THE TRIAL

For the purposes of Clinical Trial Authorisation the trial is deemed to have ended 30 days after the last patient remaining on treatment receives the last dose of Cediranib or Placebo.

For the purposes of the Main REC approval, the study end date is deemed to be the date of the last data capture.

16 PUBLICATION POLICY

The CIRCCa TMG is responsible for approving the content and dissemination of all publications, abstracts and presentations arising from the study and for assuring the confidentiality and integrity of the study. It will provide collaborators with approved publicity material and information updates at regular intervals during the course of the study. The definitive publications from CIRCCa will be written with input from the collaborators and will acknowledge all those who have contributed to the study.

No site or individual will publish data without prior approval of the TMG.

The data arising from CIRCCa will belong to Cancer Research UK Clinical Trials Unit, Glasgow. The TMG shall act as custodian of this data.

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APPENDIX I - ECOG PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance 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, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX II - DECLARATION OF HELSINKI 2008

DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and

priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result

from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

APPENDIX III - CTC AE v4.0

Please go to the following website to access the CTCAE Version 4.0.

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf.

APPENDIX IV - RECIST CRITERIA FOR ANTITUMOUR RESPONSE (RECIST Version 1.1, January 2009)

Please go to the following website to access RECIST Version 1.1, January 2009:

http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

APPENDIX V – EORTC QLQ-C30 & CX24

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birth date (Day, Month, Year): _____/_____/_____

Today's date (Day, Month, Year): _____/_____/_____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the Day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhoea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Please go on to the next page

EORTC QLQ –CX24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had cramps in your abdomen?	1	2	3	4
32. Have you had difficulty in controlling your bowels?	1	2	3	4
33. Have you had blood is your stools (motions?	1	2	3	4
34. Did you pass water/urine frequently?	1	2	3	4
35. Have you pain or a burning feeling when passing Water/urinating?	1	2	3	4
36. Have you had leaking of urine?	1	2	3	4
37. Have you had difficulty emptying your bladder?	1	2	3	4
38. Have you had swelling in one or both legs?	1	2	3	4
39. Have you had pain in your lower back?	1	2	3	4
40. Have you had tingling or numbness in your hands or feet?	1	2	3	4
41. Have you had irritation or soreness in your vagina or vulva?	1	2	3	4
42. Have you had discharge from your vagina?	1	2	3	4
43. Have you had abnormal bleeding from your vagina?	1	2	3	4
44. Have you had hot flushes and/or sweats?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4

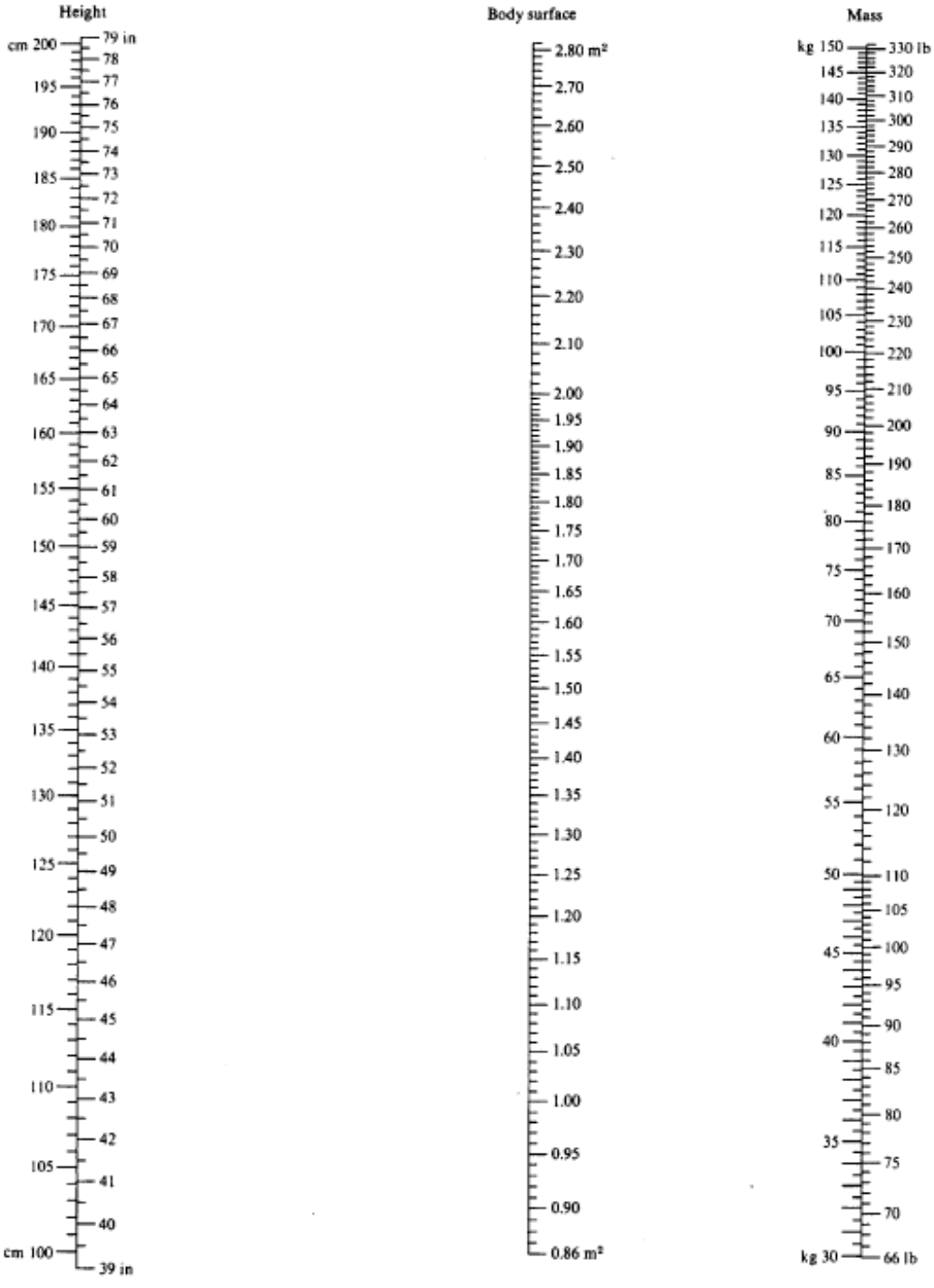
Please go on to the next page

During the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
48. Have you worried that sex would be painful?	1	2	3	4
49. Have you been sexually active?	1	2	3	4

Answer these questions only if you have been sexually active during the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
50. Has your vagina felt dry during sexual activity?	1	2	3	4
51. Has your vagina felt short?	1	2	3	4
52. Has your vagina felt tight?	1	2	3	4
53. Have you pain during sexual intercourse or other sexual activity?	1	2	3	4
54. Was sexual activity enjoyable for you?	1	2	3	4

APPENDIX VI: NOMOGRAM FOR THE DETERMINATION OF THE BODY SURFACE AREA [24]

Nomogram for determination of body surface from height and mass[†]



[†]From the formula of Du Bois and Du Bois, *Arch. intern. Med.*, 17, 863 (1916): $S = M^{0.425} \times H^{0.725} \times 71.84$, or $\log S = \log M \times 0.425 + \log H \times 0.725 + 1.8564$ (S: body surface in cm², M: mass in kg, H: height in cm).

APPENDIX VII: SOP FOR CIRCCA BLOOD SAMPLING

Introduction

The primary aim of CIRCCa-TRANS is to provide proof-of-principle for an effect of AZD2171 on targets. The secondary aim is to identify pharmacodynamic markers of response to therapy.

Patient Pathway

PTRT	Pre-treatment* - screening	LiH bloods taken
PTRT_Dup	Pre-treatment* - screening or alternative	Duplicate LiH blood taken
C1D1	C1 Day 1 – carboplatin, paclitaxel ± cediranib o.d.	Pre-dosing LiH blood taken
C1D8	C1 Day 8	LiH blood taken
C1D15	C1 Day 15	LiH blood taken
C2D1	C2 Day 1 – carboplatin, paclitaxel ± cediranib o.d.	LiH blood taken
C2D8	C2 Day 8	LiH blood taken
C3D1	C3 Day 1 – carboplatin, paclitaxel ± cediranib o.d.	Pre-dosing LiH blood taken
C4D1	C4 Day 1 – carboplatin, paclitaxel ± cediranib o.d.	Pre-dosing LiH blood taken
C5D1	C5 Day 1 – carboplatin, paclitaxel ± cediranib o.d.	Pre-dosing LiH blood taken
C6D1	C6 Day 1 – carboplatin, paclitaxel ± cediranib o.d.	Pre-dosing LiH blood taken
ETRT	End of treatment - week 22	LiH blood taken
2M	+2 months - first follow-up	LiH blood taken
4M	+4 months - second follow-up	LiH blood taken
6M	+6 months - third follow-up**	LiH blood taken

*Duplicate LiH blood sample collected pre-treatment for checking assay reproducibility

- Option 1 (preferred): collect duplicate sample on a different day from the first pre-treatment sample (collected at randomisation)
- Option 2: collect both pre-treatment samples on the same day with a *minimum* 30 minute gap between each sample (note any deviations on the plasma proforma)

**Sample collected at every visit until toxicity/ progression and subsequently if feasible.

Study Materials

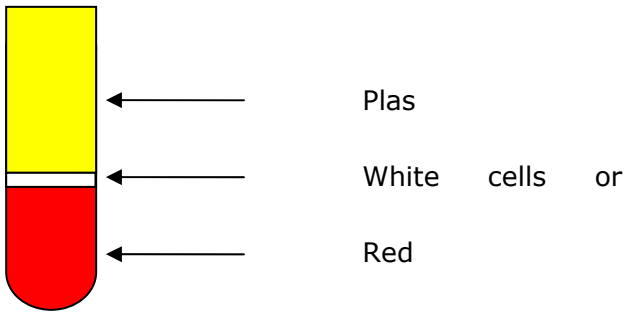
- Lithium Heparin (LiH) coated 10 ml blood tubes (green top)
- Needles & holders
- Cryovials
- Pre-printed labels

- Gilson pipette (P1000) & filter tips

Of the above materials the following will be provided to sites: Lithium Heparin coated 10ml blood tubes, cryovials and pre-printed labels.

Procedure

1. Write by hand the patient's CIRCCa Trial ID number e.g. 001005 onto pre-printed label sheet provided.
2. Each time the patient attends for blood sampling (see Patient Pathway above) a research nurse must prepare a CIRCCa-TRANS blood pack in advance (provided by Karen Carty).
3. Label 5 cryovials with the patient's CIRCCa Trial ID number (see above) on the appropriate time point label (pre-printed). Time point labels will uniquely identify each of the 5 plasma samples by giving both the patient pathway time point and the order the aliquots were collected e.g. the second plasma aliquot collected pre-treatment would be identified by PTRT_P2, and the third plasma aliquot collected at cycle 3 day 1 would be C3D1_P3.
4. Patient blood sample is taken by a phlebotomist/ research nurse using sterile technique venepuncture into a LiH blood tube. Note the time blood samples are taken on the plasma proforma. Avoid collecting the research sample before any clinical samples as it may contain tissue cells. Only at pre-treatment might two LiH blood samples be taken.
5. Within 30 minutes of collection, LiH sample must be centrifuged at 1000 g for 10 minutes at 4°C. Note: Cap the rotor buckets to minimise aerosol contamination and set brake to slow. Note the time blood samples were centrifuged on the plasma proforma. This will lead to separation into three layers as illustrated below.



N.B. Keep the pipette tip barely inserted into the plasma layer; leave behind at least 500 µl of plasma so as not to disturb the buffy layer and contaminate the sample.

6. Within 30 minutes of centrifugation, plasma should be removed in aliquots using a disposable pipette without disturbing the white or red cell layer. Aliquot the plasma layer in 500 µl volumes into appropriately labelled cryovials to a maximum of 5 vials. The first aliquot must be put into the cryovial labelled P1, the second into the cryovial labelled P2 etc. Write on the plasma proforma how many aliquots have been taken and the time plasma was aliquoted.
7. Do not try to remove all the plasma; residual plasma and the white and red cells should be discarded appropriately. Note: For the first pre-treatment sample only, please retain the red cell and buffy layers and store at -80°C.
8. Transfer the plasma aliquots to the CIRCCa-TRANS box stored in a -80°C freezer.
9. Organise via Karen Carty and the Beatson CR-UK CTU for batches of plasma samples to be couriered on dry-ice to the Paterson Institute of Cancer Research in Manchester. Batches should be sent periodically e.g. every 6 months or annually depending on recruitment. On receipt, samples will be logged and stored at -80°C.

N.B. Times post venepuncture, centrifugation speed and temperature are critical. All times must be noted on the plasma proforma and any deviations from this SOP e.g. different centrifugation speed or temperature must be clearly recorded.

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APPENDIX VIII: CIRCCA MRI SUB-STUDY PROTOCOL

Study Title:
Cediranib In Recurrent Cervical Cancer - Magnetic Resonance Imaging (CIRCCa-MRI) Evaluation of Dynamic enhanced MRI (DCE-MRI) and Diffusion Weighted (DWI-MRI) for measuring acute changes in vascular permeability and blood flow with anti-angiogenic and cytotoxic therapy in recurrent/metastatic cervix cancer

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1.0 Study Objectives

The study objectives specific to the imaging sub-protocol are:

1.1 Primary Objective

To establish multi-centre methodology and standardisation of collection of magnetic resonance imaging (MRI) parameter data in patients with cervix cancer and determining the reproducibility of the data obtained.

1.2 Secondary Objectives

1. To investigate whether there is a statistical difference in the early cediranib- induced changes in imaging parameters from baseline to day 8.
2. To demonstrate the reliability of K^{trans}, $AIUC_{60}$, ADC.

1.3 Primary Endpoints

1. To assess K^{trans} and $AIUC_{60}$ for Dynamic Contrast Enhanced – MRI (DCE-MRI).
2. To assess apparent diffusion coefficient (ADC) from the diffusion weighted imaging (DWI) analysis.

1.4 Secondary Endpoints

To assess vascular plasma volume (v_p), extravascular extracellular space volume (v_e), tumour enhancing fraction (E_F) and blood flow (F) in the DCE –MRI analysis.

2.0 Patient Population

30 patients will be invited to participate in the CIRCCa MRI sub-study who have recurrent/metastatic disease in the pelvis. It is estimated approximately two thirds of the planned 130 patients in the CIRCCa study will have disease relapse within the pelvis. Approx 7 centres will participate in the CIRCCa MRI sub-study.

2.1 Inclusion Criteria

The inclusion criteria for the MRI sub-study will be per the CIRCCa core protocol plus the additional following criteria listed specifically relating to DCE-MRI and DWI scanning.

Additional inclusion criteria specific to DCE-MRI and DWI:

1. The presence of pelvic tumour measuring 3-10 cm in diameter deemed assessable by the investigator by DCE-MRI and DWI.
2. Patient has given written informed consent to participate in the CIRCCa MRI sub-study.

2.2 Exclusion Criteria

The exclusion criteria will be as per the CIRCCa core protocol plus the additional following criteria listed specifically relating to DCE-MRI and DWI scanning:

Additional exclusion criteria specific to DCE-MRI and DWI:

1. Standard MR scanning exclusion criteria relating to metal implants ie pacemakers, metallic heart valves.
2. Known allergy to MRI intravenous contrast.
3. Renal impairment with a serum creatinine of >1.5 x ULN or a creatinine clearance of ≤ 50mL/min measured by EDTA.
4. Patients with Type II diabetes whose hypoglycaemic therapy includes metformin.

3.0 DCE-MRI and DWI

Patients will undergo three DCE-MRI and DWI scans during the study period. The scans will include two baseline scans at no more than two weeks prior to commencing treatment to establish reproducibility, and a further scan at day 8 following the commencement of treatment.

4.0 MRI Imaging Procedures

4.1 MRI Quality Assurance

A key aspect of the CIRCCa-MRI sub-study will be implementation of a quality assurance (QA) programme to ensure standardisation of acquisition and analysis methodology across centres. DCE-MRI outputs are well-known to be sensitive to variations in acquisition protocol and analysis methods. In order to reduce variability introduced by the former, all scanning sites will undergo a qualification procedure that will assess their ability to perform the necessary data acquisition protocol, including sufficiently accurate T_1 measurements, using a standard T_1 phantom (already available) that will be transported between sites. An existing ice-water DWI phantom will also be used to asses ADC measurements. A physicist will conduct a half-day scanning visit at each centre for site qualification. Each site will be visited at 3 month intervals during the study in order to reduce the risk of drift in site performance.

All data analysis, for both DCE-MRI and DWI, will also be performed in a central laboratory (www.qbi-lab.org), which will serve as the core analysis and coordinating centre. Analysis will include full quality control (QC) of the data from each site, according to established procedures. Any substandard data (e.g. inaccurate T_1 or ADC values, incorrect protocol settings, poor scanning volume selection) will be highlighted immediately to the principal and local investigators and remedial action taken. Standardisation of region of interest (ROI) delineation will be performed by trained radiography staff in the laboratory, with expert radiologist input where necessary, according to our established and effective procedures.

4.2 Data Acquistion and Data Analysis

Data acquisition

Procedures based on those published [26] will be followed at each site:

1. Localiser scans
2. T_2- weighted turbo-spin echo scan covering the same FOV as subsequent dynamic and DWI scans, but with improved spatial resolution for the purposes of defining a region of interest (ROI) around the tumour (see analysis).
3. Pre-contrast T_1- weighted acquisition with identical FOV and resolution as 2.
4. Perform a diffusion-weighted imaging scan acquired using a single-shot echo planar imaging (SS-EPI) sequence. Acquire using respiratory-triggering and five b-values (b=0,50,150, 500 and 1000) to cover the same FOV outlined in 3.
5. The dynamic scans employ a 3D T_1-weighted spoiled gradient echo sequence with variable flip angle T_1 estimation. Temporal resolution will be dependent on local scanner performance but must be no less than 6s.
6. A bolus injection of 0.1 mmol/kg Gd-DPTA (Magnevist, Bayer-Schering, Pharma AG, Berlin, Germany) is administered 15 s into the dynamic scans at a rate of 4ml/s followed by a 20ml saline flush **using a power injector (must be available at each centre).** Scan for 10 minutes in total.
7. Pre-contrast T_1-weighted acquisition with identical FOV and resolution as 2.

Data analysis

Standardised analysis procedures and data QC will be followed at the central analysis site, covering the following stages:

1. ROIs must be defined by an experienced radiologist on the T_2-w turbo spin echo scan for each patient with reference to the pre-contrast and post-contrast T_1-weighted scans. Define ROIs around the whole tumour, the rectal wall, normal bladder, any enlarged lymph nodes and the small bowel (where included in the FOV).
2. Produce ADC maps using all b-value images and at b-values above 150 in order to distinguish possible vascular and true diffusion effects. Summarise ADC values within the regions of interest using median values and generate histograms of pixel values.
3. Produce K^{trans}, $IAUC_{60}$ and other DCE-MRI parameters. Summarise parameters within the same ROIs as ADC readouts, using median values and pixel histograms.

4.3 Data Transfer

This data transfer section applies only to the blinded DCE-MRI and DWI imaging sequences and tertiary imaging data required to derive the imaging measurements. No CIRCCa clinical trial information or other patient information will be transferred to the QBI laboratory.

Image data will be transferred to the QBI Laboratory located in the Imaging Science and Biomedical Engineering Research Group, University of Manchester by copying the blinded scan data from the MRI scanner onto CD. Each patient will be allocated an imaging number and any data presented or referred to will be identified using this imaging number solely.

4.4 Data Analysis and Storage

Analyses will be performed by The University of Manchester and additional statistical analysis as appropriate using SAS or S-Plus software. The data will be stored in the secure study-specific filing drawer in the QBI Laboratory. Access to the data and to the room is by study personnel only.

After the trial has been signed off, data and all study-specific documents will be archived in a secure, fire-proof location at the University of Manchester.