Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012;366:883-92.

Protocol for Investigator-Initiated Study

A Phase II Study Of Everolimus Therapy Before Nephrectomy In Metastatic Renal Cell Cancer

Signature_____

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Summary of Protocol

PRODUCT	Everolimus
PROTOCOL NUMBER	CCR 3259
PROTOCOL TITLE	A Phase II Study Of Everolimus Therapy Before Nephrectomy In Metastatic Renal Cell Cancer
TARGET DISEASE	Metastatic Renal Cell Carcinoma
STUDY SITE	Royal Marsden Hospital
PATIENT POPULATION	Patients (n=40) with metastatic renal cell carcinoma of predominant clear cell histology suitable for cytoreductive nephrectomy
STUDY OBJECTIVES	To evaluate safety, toxicity and changes in biomarkers before and after therapy with everolimus at a dose of 10mg per day for 6 weeks prior to nephrectomy
STUDY DESIGN	Participants to undergo biopsy of primary tumour followed by 6 weeks of everolimus therapy followed by nephrectomy. Everolimus to be continued post-operatively.
TREATMENT REGIMEN	Everolimus 10mg once daily continuously
ROUTE OF ADMINISTRATION	Oral
PRIMARY ENDPOINTS	Safety profile of everolimus given pre- and post nephrectomy in metastatic renal cell carcinoma
SECONDARY ENDPOINTS	Changes in biomarkers, MR functional imaging, response rate, progression free and overall survival

Abbreviations

CRF	Case Report Form
GCP	Good clinical practice
IFNα	Interferon alpha
NCI-CTC	National Cancer Institute Common Terminology Criteria
OS	Overall Survival
PDGF	Platelet-Derived Growth Factor
PFS	Progression-Free Survival
RCC	Renal cell carcinoma
VEGF	Vascular Endothelial Growth Factor

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1 Background

Introduction

Renal cell carcinoma (RCC) is diagnosed in over 6000 patients and accounts for approximately 3% of malignant disease annually in the UK (CRUK CancerStats Monograph 2004). Many patients initially present with advanced or unresectable disease and furthermore up to 30% of patients treated by nephrectomy with curative intent for localised disease will relapse [1]. The 5-year survival rate for metastatic RCC is less than 10%. The prognosis for metastatic RCC is poor with a median survival of 6-8 months [2] and reported response rates to chemotherapy [3] and hormonal agents [4] have been of the order of only 5-10%. Approximately half of RCC tumours have mutations in the Von Hippel-Lindau gene (VHL). VHL loss increases expression of the hypoxia-inducible factor alpha transcription factors (HIF-1□ and HIF-2□). These factors regulate the expression of vascular endothelial growth factor (VEGF) and other molecules implicated in angiogenesis and invasion. These pathways are important in the pathophysiology of RCC although their roles are understood incompletely.

Surgical Treatment of Metastatic Renal Cell Carcinoma

The mainstay of curative treatment for renal cell carcinoma is surgery; nephrectomy has also been shown to be of palliative benefit in metastatic disease. Two phase III trials, European Organization Research and Treatment of Cancer 30947 [5] and Southwest Oncology Group 8949 [6], have demonstrated a survival benefit for nephrectomy followed by interferon versus interferon alone in patients with an excellent performance status. Nephrectomy is generally a relatively safe and well-tolerated operation in experienced hands: a report from Memorial Sloan Kettering Cancer Centre of 692 radical nephrectomies for renal cell cancer performed between 1995 and 2002 quotes a 3% procedure-related complication rate and 0.2% procedure-related mortality [7].

Medical Treatment of Metastatic Renal Cell Carcinoma

Metastatic clear cell renal carcinoma generally is resistant to chemotherapy. Cytokine-based therapies therefore have been used in the treatment of metastatic RCC but with limited anti-tumour effect. For example, interferon-α (IFN-α) has a response rate of approximately 10 – 15% in appropriately selected individuals [8].

Randomised trials reported in the last 5 years have demonstrated that a number of agents such as the monoclonal antibody bevacizumab [9] and the kinase inhibitors everolimus, sorafenib, sunitinib and temsirolimus are active in advanced RCC. Bevacizumab is directed against vascular endothelial growth factor (VEGF), a key mediator of angiogenesis, whilst sorafenib and sunitinib inhibit a number of targets including the VEGF and platelet-derived growth factor (PDGFR) receptor tyrosine kinases. Everolimus and temsirolimus inhibit the intracellular mammalian target of rapamycin (mTOR) kinase. Sunitinib [10] and temsirolimus [11] have demonstrated efficacy in comparison with immunotherapy in the 1st line setting in patients with favourable and poor prognosis advanced disease respectively. Sorafenib has demonstrated efficacy in comparison with placebo in the 2nd line setting in patients with immunotherapy-refractory disease [12]. Everolimus is active in patients that have progressed despite therapy with sorafenib or sunitinib [13].

Pre-operative Systemic Therapy

There is no standard pre-operative systemic therapy in metastatic RCC but pre-operative medical therapy is used widely in the treatment of cancer. The potential advantages of this approach are threefold. The first is disease down-staging, allowing less radical surgical approaches with possible benefits in terms of surgical morbidity and/or cosmesis (e.g. lumpectomy versus mastectomy for breast cancer). The second advantage is in terms of in vivo sensitivity testing i.e. is the cancer sensitive to the treatment? This may be important for the selection of post-operative adjuvant therapy in as much as tumours sensitive to a given therapy pre-operatively may logically be treated post-operatively with the same therapy. Conversely, tumours that are not sensitive to a given pre-operative therapy may better be treated post-operatively with an alternative therapy. Third, candidate markers of response and resistance may be assessed using pre-operative therapy i.e. a parameter may be measured both prior to and during treatment and correlated with clinical outcome either early (which markers correlate with response to a given neoadjuvant therapy?) or late (which markers correlate with overall survival or likelihood of relapse?). Such markers, after validation, may subsequently be used to tailor therapy to individual tumours or to individual patients in both adjuvant and metastatic settings and may give insight into in vivo mechanisms of drug action.

Everolimus

Everolimus (RAD001) is an oral mTOR inhibitor and blocks progression from the G1 to the S phase of the cell cycle; it is thought that as a result everolimus may play a role in VEGF inhibition. The mammalian target of rapamycin (mTOR) is an intracellular serine/threonine protein kinase and a component of the phosphatidylinositol 3-kinase (PI3K) / protein kinase B (AKT) / mTOR pathway. Everolimus inhibits mTOR through association with the FK506-binding protein-12 (FKBP12). The mTOR protein can complex with raptor (regulatory-associated protein of mTOR) to form mTOR Complex 1 (mTORC1) and with rictor (rapamycin-insensitive companion of mTOR) to form mTOR Complex 2 (mTORC2). The mTORC1 protein can be activated by nutrients via the PI3K pathway and by growth factor receptors such as the epidermal growth factor receptor (EGFR), insulin growth factor receptor (IGFR), platelet-derived growth factor receptor (PDGFR) and vascular endothelial factor growth factor receptor (VEGFR).

The downstream effects of mTORC1 activation are mediated by the phosphorylation of a number of substrates such as ribosomal p70 S6 kinase 1 (S6K1), the complex of eukaryotic initiation factors 4E, 4F and 4G (eIF-4E, eIF-4F and eIF-4G) and the binding protein of eIF-4E (4E-BP1), leading to protein synthesis and progression from the G1 to the S phase of the cell cycle [14]. Everolimus binds only to mTORC1 and is not known to have any other targets in contrast to kinase inhibitors such as sorafenib, sunitinib, imatinib and erlotinib that have a number of cellular targets [15]. It is unclear why mTORC1 is an important target in renal cell carcinoma [13] although anti-VEGF therapy such as the monoclonal antibody bevacizumab [9, 16] and the anti-VEGFR/PDGFR therapies sunitinib [10] and sorafenib [12] are active in advanced renal cell carcinoma and it may be that mTOR inhibition targets the same signalling pathways albeit further downstream [17]. It is noteworthy that inhibition of signalling in these pathways may result in therapeutic activity in advanced renal cell carcinoma via effects in the non-tumour compartment e.g. vascular cells such as endothelial cells and pericytes, rather than in the tumour compartment.

Preclinical data

Everolimus has anti-proliferative effects in vitro against a number of tumour cell lines in cell culture and in animal xenograft models [18-20]. Boulay and colleagues have described a syngeneic rat tumour xenograft model in which daily and weekly administration of everolimus was investigated [20]. Dose-dependent anti-tumour activity was reported with both schedules and treatment was well tolerated. Phosphorylation of the eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and inactivation of the ribosomal p70 S6 kinase 1 (S6K1) was evaluated in skin, peripheral blood mononuclear cell (PBMC) and tumour extracts. Suppression of tumour growth correlated with inhibition of S6K1 in PBMCs, raising the possibility this marker may be a surrogate for anti-tumour efficacy for everolimus. Interestingly, animal data have also demonstrated that inhibition of S6K1 in PBMCs correlates with S6K1 inhibition in xenografted breast cancer tumours in nude mice treated with temsirolimus [21].

Clinical data: dosing, pharmacodynamics and biomarkers

Two phase I studies evaluating the dosing, toxicity, pharmacodynamics and potential biomarkers of everolimus in advanced cancer have been published [22, 23].

In a study reported by O'Donnell and colleagues [22], 92 patients were treated on daily (n=37) and weekly (n=55) schedules of everolimus. Ribosomal p70 S6 kinase 1 (S6K1) in PBMCs was measured in patients treated with weekly everolimus up to a dose of 30mg/week and 20mg/week was identified as the dose causing sustained inhibition of this target. A maximum tolerated dose of everolimus was not defined and doses of 5mg daily and 20mg weekly were recommended for further study; dose-limiting toxicity was seen in one patient at 50mg/week (stomatitis and fatigue) and another patient at 10mg/day (hyperglycaemia).

Tabernero and colleagues [23] treated 55 patients on daily schedules of 5mg or 10mg and weekly schedules of 20mg, 50mg or 70mg of everolimus. Dose-limiting toxicity was seen in one patient at 10mg/day (grade 3 stomatitis) and 4 patients (of 7 treated) at 70mg/week (2 with grade 3 stomatitis, 1 with grade 3 hyperglycaemia and 1 with grade 3 neutropaenia). Skin and tumour biopsies were taken and assayed immunohistochemically for total and phosphorylated S6K1, 4E-BP1, eIF-4G, AKT and for Ki-67. Overall, statistically significant decreases in the expression of phosphorylated S6K1 and eIF-4G in skin and tumour and a similar reduction in 4E-BP1 in skin but a statistically non-significant reduction in tumour were noted. Inhibition of phosphorylated S6K1 expression was reported at daily doses of 5mg and 10mg of everolimus but complete inhibition of phosphorylated eIF-4G expression was noted only at the 10mg daily dose level. Similarly, inhibition of phosphorylated S6K1 expression was reported at all weekly doses evaluated but complete inhibition of phosphorylated eIF-4G expression was noted only at the 50mg and 70mg weekly dose levels. Doses of 10mg daily and 50mg weekly were therefore recommended for further evaluation.

Clinical data: toxicity

In addition to the phase I studies already discussed, a clinical trial of everolimus as a single agent for the treatment of advanced renal cell carcinoma has been reported by Motzer and colleagues. In this study, 410 patients with advanced renal cell carcinoma who had failed prior treatment with sorafenib or sunitinib were treated with everolimus at a dose of 10mg daily or placebo [13].

In the phase I study reported by O'Donnell and colleagues [22], fatigue was seen in 31 patients (34%) with severe fatigue in only 2 patients . Rash occurred in 44 patients (48%); only 1 patient had a grade 3 rash which improved to grade 1 on dose interruption and dose reduction of everolimus. Rash was generally noted on the face and upper body. Gastrointestinal side effects such as stomatitis, nausea, vomiting, anorexia, constipation, abdominal pain and distension were reported in 61 patients (66%) with grade 3 stomatitis in 3 patients. Hyperglycaemia and hyperlipidaemia were each reported in 7 patients; 3 patients had grade 3 hyperglycaemia and 2 patients had grade 3 hyperlipidaemia. Haematological toxicities were relatively uncommon. Infections such as pneumonia, rhinitis, cutaneous herpes simplex and oral candidiasis complicating stomatitis were reported in 12 patients and thought related to everolimus administration. No drug-related fatalities occurred. In the phase I study reported by Tabernero and colleagues [23], fatigue, rash and stomatitis were reported in approximately one third of patients. Haematological toxicity was again uncommon and grade 3 toxicities were reported in 9 patients (16%) including fatigue, stomatitis and hyperglycaemia.

Treatment in the phase III study in advanced RCC was generally well tolerated; toxicity led to the discontinuation of therapy in 10% of patients receiving everolimus (most often because of fatigue, dyspnoea, 'lung disorder' and pneumonitis) and 4% of patients receiving placebo. Stomatitis (40% in the everolimus group vs 8% in the placebo group), rash (25% vs 4%) and fatigue (20% vs 16%) were again the commonest toxicities but were generally mild or moderate in severity; less than 5% of patients had grade 3 stomatitis, rash or fatigue. Anorexia, diarrhoea, nausea and vomiting of mild or moderate severity were reported in between 10 and 20% of patients. Infections and non-infectious pneumonitis were commoner in the everolimus group than the placebo group: 10% vs 2% for infections and 8% vs none for pneumonitis. Grade 3 pneumonitis was reported in 3% and grade 3 or 4 infections in 4% of study participants receiving everolimus; there were no grade 3 or worse infections or pneumonitis in the placebo group. Pneumonitis generally resolved on discontinuation of everolimus. All deaths on the study were attributable to progressive renal cell carcinoma except 1 death from myocardial infarction in the placebo group and 1 death from overwhelming candidal sepsis and acute respiratory failure in the everolimus group.

Laboratory abnormalities were relatively common but again generally mild or moderate in severity. The most marked laboratory abnormalities noted were again related to glucose and lipid metabolism: hypertriglyceridaemia and hypercholesterolaemia were both reported in over 70% of patients (in comparison with just over 30% of controls) although less than 5% had grade 3 toxicity. Hyperglycaemia was reported in 50% of cases (12% grade 3) in comparison with 23% in the placebo group (1% grade 3).

Clinical data: efficacy

In a phase II study in metastatic RCC reported in abstract form (Jac et al, ASCO 2007, Abstract 5107), treatment with everolimus resulted in a partial response to treatment in 12/37 patients (32%). Nineteen patients (51%) experienced disease stabilisation for at least 3 months. Most patients (n=31) had received prior therapy. The phase III study discussed above [13] demonstrated that everolimus also prolongs progression-free survival in comparison with placebo in patients with advanced disease with progression after anti-VEGF therapy. Everolimus is consequently now considered the standard treatment option in this setting and is under investigation in randomised trials in the first line setting.

Conclusions and Study Rationale

Nephrectomy for RCC results in clinical benefit in carefully selected patients even in the setting of metastatic disease. Everolimus is well tolerated and has demonstrated a high response rate in metastatic RCC but the mechanism of action in vivo remains to be established. A clinical trial of everolimus in patients with metastatic RCC prior to nephrectomy offers a unique opportunity to compare tumour samples before and after treatment. Targets for everolimus in RCC in vivo can thereby be identified and changes in biomarkers correlated with both response to treatment and toxicity. This approach may also give insight into in vivo mechanisms of drug action and will also allow the correlation of pathological response at surgery with subsequent clinical response; the latter may give some insight into the pathophysiology of disease stabilisation that is often seen with everolimus and similar drugs. If significant activity is seen in the primary lesion then there may be a role for everolimus in the primary medical therapy of locally advanced renal cell carcinoma.

Given the fact that there is limited experience of the use of mTOR inhibitors pre-operatively in patients with advanced cancer, this study has been designed as a phase II study in order primarily to investigate the safety of this approach. The efficacy of therapy in terms of response rate and survival will also be investigated as will biomarkers in tumour and in circulating tumour cells (CTCs). Functional imaging will be correlated with both clinical response and changes in tissue biomarkers.

2 Study Objectives

Primary objective

The primary objective of this study is to define the safety of everolimus given pre- and post operatively to patients with metastatic renal cell carcinoma undergoing nephrectomy.

Secondary objectives

The secondary objectives of this study are to determine toxicity, response to treatment, progression free and overall survival.

Exploratory objectives

The exploratory objectives of this study are to correlate changes in biomarkers with toxicity, response to treatment and survival and to evaluate changes in magnetic resonance functional imaging characteristics of the tumour before and after 6 weeks of everolimus therapy and at disease progression.

3 Study Endpoints

Primary endpoint

The safety profile of everolimus given pre- and post operatively to patients with metastatic renal cell carcinoma undergoing nephrectomy

Secondary endpoints

Response rate, progression free and overall survival

Toxicity of everolimus (by NCI CTC grading version 3.0)

Changes in magnetic resonance functional imaging characteristics of the tumour before and after 6 weeks of everolimus therapy and at disease progression

Molecular and pathological changes in biomarkers as a consequence of everolimus therapy

4 Inclusion Criteria

Histologically confirmed metastatic renal cell carcinoma

At least one site of disease outside the kidney measurable per RECIST

Scheduled to undergo nephrectomy as part of treatment plan

No prior systemic therapy for renal cell carcinoma

Male or female, 18 years of age or older

Life expectancy of 12 weeks or greater

ECOG performance status 0 or 1

Serum aspartate transaminase (AST) serum alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN), or AST and ALT≤5 x ULN if liver function abnormalities are due to underlying malignancy

Total serum bilirubin ≤1.5 x ULN

Serum creatinine ≤1.5 x ULN

Absolute neutrophil count (ANC) ≥1500/µL

Platelets ≥100,000/µL

Haemoglobin ≥9.0 g/dL

Prothrombin time (PT) ≤1.5 x ULN

Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrollment

Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures

5 Exclusion Criteria

Intracranial disease, unless there has been radiological evidence of stable intracranial disease > 6 months. In the case of a solitary brain metastasis, evidence of a disease-free interval of at least 3 months post surgery. All patients previously treated for brain metastases must be stable off corticosteroid therapy for at least 28 days

Need for nephrectomy to relieve symptoms relating to the primary tumour or for emergency nephrectomy

Diagnosis of any second malignancy within the last 5 years, except for adequately treated basal cell carcinoma, squamous cell skin cancer, or in situ cervical cancer

Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness

Pregnancy or breastfeeding. Female patients must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of therapy. All female patients with reproductive potential must have a negative pregnancy test (serum or urine) prior to enrollment. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy

Current signs or symptoms of severe progressive or uncontrolled hepatic, haematologic, gastrointestinal, endocrine, pulmonary or cardiac disease other than directly related to RCC

6 Study Design

This is a multicentre centre Phase II trial. The primary endpoint is the safety of pre-operative and post-operative everolimus therapy in 19 evaluable patients undergoing cytoreductive nephrectomy for metastatic renal cell carcinoma of predominant clear cell histology (Stage A). Subject to review by the data monitoring committee, a further 21 patients will be enrolled in an expansion phase (Stage B) to gain further safety, efficacy, toxicity data and to validate biomarker data gained from the first 19 patients.

After giving informed consent to enter the study, participants will undergo baseline CT scanning, pulmonary function tests, blood sampling for circulating tumour/endothelial cells (CTCs/CECs) and MR functional imaging. Biopsy of the primary lesion and appropriate metastatic lesions will then be undertaken and samples sent for both histopathological and molecular analyses. It is very likely that a small number of patients will not have predominant clear cell histology but this will not preclude study entry. The study will however recruit 40 evaluable patients with predominantly clear cell histology.

Participants will be treated with everolimus 10mg orally daily for 6 weeks with repeat CT scanning, functional imaging and CTC/CEC sampling after 6 weeks. Cytoreductive nephrectomy will be carried out 1 week after stopping everolimus and molecular analyses carried out on the nephrectomy specimen. Everolimus will be continued post-operatively in all patients that derived benefit from pre-operative treatment. This will be continued as long as study participants are deriving benefit from treatment and further biopsies will be carried out at disease progression. Response to everolimus in the nephrectomy specimen and in other marker lesions will be correlated with changes in biomarkers, CTCs/CECs and functional imaging parameters.

7 Study Plan

A cycle of therapy is defined as 28 days of treatment with everolimus. Please refer to Appendix D.

The following screening procedures must be performed between 21 and 3 days prior to treatment with everolimus:

Patient signature on consent form for study entry and biopsy

Medical history and physical examination including assessment of concomitant medications

ECOG performance status, body weight, height, and vital signs (temperature, blood pressure, heart rate, respiratory rate)

Haematology, coagulation, glucose, renal and liver function, serum calcium and LDH, lipid profile, HbA1c

Urinalysis

Pregnancy test (serum or urine), if applicable

CT thorax, abdomen and pelvis

Lung function tests

MR functional imaging (to be done before biopsy: see Appendix E)

Tumour biopsy via appropriate (US or CT) guidance at least 3 days prior to starting everolimus (see Appendix E)

It is suggested that functional imaging and CT thorax, abdomen and pelvis are carried out on the same day just prior to biopsy approximately 1 week before everolimus is started

The following must be performed on **cycle 1 day 1** prior to starting the study drug:

Confirmation of histological diagnosis of metastatic renal cell carcinoma

Medical history and physical examination including assessment of concomitant medications

ECOG performance status, body weight, and vital signs

Haematology and blood chemistry as above

Blood sample for biomarker analysis (see Appendix E)

Haematology and blood chemistry as above

Dispense everolimus to patient to start the same day

Cycle 2, Day 1 (day 29):

Medical history and physical examination including assessment of concomitant medications

ECOG performance status, body weight, and vital signs

Haematology and blood chemistry as above

Lung function tests

Blood sample for biomarker analysis (see Appendix E)

Cycle 2, Day 15 (day 43):

Stop everolimus (last dose on cycle 2 day 15)

Medical history and physical examination including assessment of concomitant medications

ECOG performance status, body weight, and vital signs

Haematology and blood chemistry as above

Lung function tests

Blood sample for biomarker analysis (see Appendix E)

Cycle 2, Day 15 to Day 22:

CT thorax, abdomen and pelvis

MR functional imaging (see Appendix E)

Cycle 2 Day 22:

Medical history and physical examination including assessment of concomitant medications

ECOG performance status, body weight, and vital signs

Haematology and blood chemistry as above

Blood sample for biomarker analysis (see Appendix E)

Patient undergoes nephrectomy

Nephrectomy specimen sent for translational research studies (see Appendix E)

Surgeon completes case report form re: surgical aspects of nephrectomy

Anaesthetist completes case report form re:need for blood transfusion and blood pressure control

Patient discharged from hospital when medically fit i.e. 5-10 days postoperatively

Cycle 3 day 1 (and subsequent cycles until disease progression):

Cycle 3 day 1 is defined as the day on which the study participant has recovered sufficiently from nephrectomy to restart everolimus

Medical history and physical examination including assessment of concomitant medications

ECOG performance status, body weight, and vital signs

Haematology and blood chemistry as above

CT thorax, abdomen and pelvis within 1 week of cycle 3 day 1

Blood sample for biomarker analysis (see Appendix E)

Dispense everolimus to the patient to start the same day

Subsequent tumour imaging to be performed prior to cycle 5 day 1 and prior to odd cycles i.e. 7, 9, 11 etc

Procedure at disease progression:

Medical history and physical examination including assessment of concomitant medications

ECOG performance status, body weight, and vital signs

Haematology and blood chemistry as above

Blood sample for biomarker analysis (see Appendix E)

MR functional imaging (to be done before biopsy: see Appendix E)

Tumour biopsy via appropriate (US or CT) guidance; sample for translational research studies (see Appendix E)

8 Therapeutic regimen and dose modifications

Everolimus will be given at 10mg once daily continuously. The drug will be stopped after 6 weeks and nephrectomy undertaken 1 week later. Everolimus will be restarted at such time as the study participant has recovered sufficiently from nephrectomy (normally 2 to 4 weeks post-operatively and defined for the purposes of this study as cycle 3 day 1) and continued as long as the study participant is deriving clinical benefit from therapy. A cycle of treatment is defined as 28 days.

Dose Interruption and Reduction

Everolimus will be stopped the event of significant toxicity and restarted if appropriate when toxicities have resolved. On restarting, dose can be reduced to 5mg once daily (dose level -1) and to 5mg on alternate days (dose level -2) in the event of significant toxicity. Recovery to acceptable levels of toxicity must occur within 4 weeks to allow continuation in the study. No more than 2 dose reductions are permitted in any patient. If further dose reduction is required, the patient must be discontinued from the study.

Dose Re-Escalation

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

Duration of Therapy

Treatment cycles will be repeated until the patient is no longer gaining benefit unless unacceptable toxicity is encountered.

Patients may also discontinue protocol therapy in the following instances:

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

Request by patient

Concomitant therapy

Everolimus is metabolised primarily by liver enzymes, in particular CYP3A4. Agents known to induce CYP3A4 including dexamethasone should be avoided. Agents known to inhibit this enzyme (eg, grapefruit juice) should also be avoided. No other approved or investigational systemic anticancer treatment will be permitted during the study period, including chemotherapy, hormone therapy and immunotherapy. No other investigational drug may be used during treatment on this protocol, and concurrent participation in another clinical treatment trial is not allowed. Other concomitant therapies considered necessary for the patient's well being may be prescribed at the investigator's discretion. Every medication or treatment taken by the patient during the trial, the duration of treatment and the reason for its administration must be recorded on the case report form (CRF).

Surgery

Enrollment into the trial will not affect any aspect of the surgical treatment plan and each patient will be treated according to local practice in terms of procedure e.g. open vs laparoscopic nephrectomy. Patients will be admitted to hospital 2 days prior to surgery for review and there will be close liaison between the trial research nurse and anaesthetic and surgical teams with regard to possible drug-related side effects such as infection risk and pneumonitis. Nephrectomies on trial patients will also be audited monthly at MDT meetings.

9 Statistical considerations

Sample size calculation

The sample size calculation is based on a Simon optimal two-stage design using a type I error level of 5% and power of 80%. We assume the treatment to be acceptable if less than 1% (P1=0.99) of patients experience non-haematological grade 4 toxicity or death due to the drug. If more than 10% (P0=0.90) of patients experience grade 4 non-haematological toxicity or death, the treatment is unacceptable. Nineteen patients will be treated in Stage A of this study. If no more than 2 of these patients experience grade 4 toxicity or death possibly related to everolimus, the trial will continue. If a further 21 patients are treated in Stage B (n=40 in total) and no more than 3 patients in total experience grade 4 toxicity or death related to everolimus, we will be able to conclude, subject to the parameters above, that the real risk of grade 4 toxicity or death attributable to the administration of everolimus in this setting is less than 10% (but please see below for details on cohort design and early stopping rules).

Study Conduct

This trial is designed to assess the safety of everolimus in patients with advanced renal cell carcinoma undergoing nephrectomy. The study has a two-stage design with 19 patients to be treated in Stage A and 21 patients in Stage B. Patients in Stage A will be treated in 3 consecutive cohorts to evaluate the safety of everolimus using the same dose for each cohort. Patients in Stage B will be treated in one cohort.

Pre-determined early stopping rules will be applied to protect patients against undue toxicity attributable to everolimus. These rules will be applied from the first day of treatment with everolimus (cycle 1 day 1) to the 30th post-operative day.

The stopping rules are as follows:

The study will be terminated at any time if 1 patient experiences non-haematological grade 4 toxicity or dies in circumstances probably related to everolimus therapy

In Stage A, the study will continue if 1 patient experiences non-haematological grade 4 toxicity or dies in circumstances possibly related to everolimus therapy

In Stage A, the study will be terminated if a 2nd patient experiences non-haematological grade 4 toxicity or dies in circumstances possibly related to everolimus therapy

In Stage B, the study will continue if a 2nd patient experiences non-haematological grade 4 toxicity or dies in circumstances possibly related to everolimus therapy

In Stage B, the study will be terminated if a 3rd patient experiences non-haematological grade 4 toxicity or dies in circumstances possibly related to everolimus therapy

In Stage A, 1 patient will be treated in the 1st cohort.

In Stage A, the 2nd cohort will not open until the patient in cohort 1 has reached the 30th post-operative day. Three patients will be treated in the 2nd cohort, starting therapy not less than 2 weeks apart.

In Stage A, the 3rd cohort will not open until the third patient in cohort 2 has reached the 30th post-operative day. Fifteen patients will be treated in the 3rd cohort at intervals not less than 2 weeks apart.

In Stage B, all patients (n=21) will be treated in the same cohort at intervals not less than 2 weeks apart.

The data monitoring committee (DMC) will meet after the final patient in each cohort has reached the 30th post-operative day. The DMC will also meet within 1 week of any grade 4 non-haematological toxicities or deaths whether thought attributable to everolimus or not.

Primary Analyses

Safety will be assessed by a summary of adverse events and by the proportion of patients experiencing all grades of toxicity (with 95% confidence intervals). Toxicities will be tabulated (by grade) using the NCI Common Terminology Criteria for Adverse Events (version 3.0).

Patient demographic and baseline characteristics (age, sex, ECOG performance status, number of metastatic sites etc.) will be summarized as frequency counts or means (and ranges) and medians (and interquartile ranges), depending on whether the variable is categorical or continuous.

Secondary Analyses

The percentage of patients with complete tumour response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) will be tabulated. Associated 95% CI will be provided for response rates. The duration of objective response (for patients with CR and PR) will be defined as the time from initial CR or PR to the time of disease progression or death (whichever occurs first). For patients who do not die or experience PD, duration of objective response will be censored on the day of the last tumour assessment.

Progression-free survival (PFS) will be defined as the time from the first day of everolimus treatment (cycle 1 day 1) until documented disease progression or death (whichever occurs first). Patients who do not have documented PD or death will be censored on the day of last tumour assessment (last follow-up). Overall survival will be measured from the first day of everolimus treatment until death or last follow-up. PFS and overall survival will be presented graphically using the Kaplan-Meier method. Median time to event and 95% CI will be estimated from the Kaplan-Meier curves.

Exploratory Analyses

Biomarker analyses will be performed separately (see Appendix E). Statistical analyses will be performed using R 2.8.0.

10 Data Handling and Record Keeping

Protocol-specified source documents (e.g., hospital discharge summaries, operative/procedural reports and investigation results) and copies of all CRFs and study-related documentation must be retained at the site.

The investigator shall maintain the records of drug disposition, final CRFs, worksheets and all other study-specific documentation, e.g. Study File notebooks and source documentation until notified by the sponsor that records may be destroyed.

To avoid error, the investigator should contact Novartis before the destruction of any records pertaining to the study to ensure they no longer need to be retained.

11 Sponsor

The Royal Marsden Hospital will be sponsor of the study and will fulfil the sponsor responsibilities as defined in all applicable Regulations and EU Directives. Novartis will only be responsible for providing financial assistance and supply of everolimus in bulk.

12 Publication Policy

Novartis and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Novartis and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. The aim of this study is to publish a combined clinical and scientific manuscript; the 1st author of this will be Dr James Larkin and the senior author Dr Charles Swanton.

13 Ethical and legal aspects

Independent Ethics Committee

The appropriate Ethics Committees at the Royal Marsden Hospital must approve the protocol and informed consent documents, agree to monitor the conduct of the study, and agree to review study progress periodically, at intervals not to exceed one year. The investigators will provide Novartis or their designee with documentation that the Ethics Committees have approved the study before the study may begin. An informed consent form will be prepared according to the institutional requirements for informed consent and the applicable regulations.

In addition, the investigators must provide the following documentation to Novartis or their designee:

the Ethics Committee's annual reapproval of the protocol

the Ethics Committee's approval of revisions to the informed consent documents or any amendments to the protocol. Any revisions to the protocol that may increase patient risk exposure must be approved prior to implementation. Administrative changes (such as a change in address or phone number) must be sent to the Ethics Committee but do not require their approval. The investigators will provide Novartis or their designee with documentation of all approvals.

Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, the trial statistician and the trial co-ordinator. Notwithstanding the legal obligations of the Co-Sponsors and Chief Investigator, the TMG will have operational responsibility for the conduct of the trial. The Committee's terms of reference, roles and responsibilities will be defined in a charter based on MRC Good Clinical Practice (MRC GCP).

Data Monitoring Committee

A data monitoring committee (DMC) will be established. The DMC will consist of a statistician (Karen Thomas) and 4 clinicians (Christopher Woodhouse (chair), Sanjay Popat and Ian Chau) who will review, on a regular basis, accumulating safety data from the study. The DMC will also be notified of protocol amendments. The DMC will advise with regard to:

the continuing safety of current and future participants in the study

the continuing validity and scientific merit of the study

The DMC will meet after the final patient in each cohort has reached the 30th post-operative day. The DMC will also meet within 1 week of any grade 4 toxicities or deaths whether thought attributable to everolimus or not. The DMC will subsequently convene at their discretion at a minimum of quarterly per year; more frequent meetings will be dictated by the availability and severity of ongoing safety information.

The DMC will review all safety information to determine whether the study will continue unchanged or whether protocol modifications are required to ensure patient safety. In addition, the DMC will monitor the patient dropout rate and will, in the event of excessive

patient dropout, have the authority to ask for increased enrollment in order to maintain the power of the study. Recommendations for closing should be on the basis of excessive toxicity in the q3 month statistics report or the aggregated safety data. This determination will be documented by a letter from the DMC.

Insurance

NHS Indemnity Statement

Where the Royal Marsden NHS Foundation Trust is either sponsoring or collaborating with externally sponsored research the NHS Litigation Authority will cover standard clinical negligence by employees, staff and health professionals employed by the Royal Marsden NHS Foundation Trust.

For more information visit the following website:

www.clinical-medical-negligence-injuries.co.uk

There is unlimited liability and no excess.

Insurance is provided under the Clinical Negligence Scheme for Trusts and there is no cover for non-negligence claims.

For all notification of claims please contact the Board Secretariat.

Patient Information and Consent

The consent form will be reviewed with the prospective study patient or their legal representative, and the investigator will be available to answer questions regarding procedures, risks, and alternatives. The Chief Investigator or his designee (as defined on the Delegation List) will obtain written informed consent from each patient or from the patient's legal representative or designee as defined by local law. Consent will be obtained before any protocol-specific procedures are performed.

Confidentiality

All records identifying the patients will be kept confidential and to the extent permitted by the laws/regulations, will not be made publicly available. Only the patient number and patient initials will be recorded in the case report forms. Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed in writing that representatives of the sponsor, Novartis (or their designee), the Ethics Committee and other regulatory authorities may inspect their medical records to verify information collected and that all personal information made available will be handled in the strictest confidence and in accordance with local data protection laws. If the results of the study are published, the identity of the patients will remain confidential.

Regulatory Requirements and GCP

The investigators are responsible and will warrant that their study conduct will be compliant to principles of GCP, local regulatory requirements and with the Ethics Committee-approved research protocol.

Monitoring

Details of on-site monitoring at the Royal Marsden and other sites are to be inserted on the conclusion of discussion between Dr Larkin and Jane Lawrence.

Funding

The studied will be supported in part by educational grants from Novartis and everolimus will be provided free of charge by Novartis.

Appendix A References

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Appendix B Adverse Event Reporting and Follow Up

Key definitions

Adverse Event (AE)

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. For example, an AE can be any unfavourable or unintended sign such as an abnormal laboratory finding, symptom or disease which may or may not be considered related to the Investigational Medicinal Product (IMP).

Adverse Reaction (AR)

Any untoward and unintended response in a subject to an IMP which is related at any dose administered to that subject. Any adverse event which is assessed by the C.I or treating clinician as having a reasonable causal relationship with the IMP will be classed as an Adverse Reaction.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any untoward medical occurrence or effect that at any dose that results in:

death

is life-threatening*

requires hospitalisation or prolongation of existing hospitalisation

results in persistent or significant disability or incapacity

is a congenital anomaly or birth defect

is an important medical event

*Life threatening: In the definition of an SAE or an SAR, refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgement should always be used to decide whether an adverse event or adverse reaction is serious. For example any adverse event which may jeopardise the subject or requires any medical intervention should also be considered serious, even if the situation is not life-threatening or requires hospitalisation.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a SAR that is classified as unexpected i.e a serious adverse reaction in which the nature or severity is not consistent with the information about the medicinal product described in the SPC or IB. Therefore, the event is suspected to be related to the drug and is unexpected according to is safety profile.

Serious Expected Events

A serious expected event is an adverse event/reaction meets the definition of serious and is a consistent with the SmPC for everolimus. Expected events for this study will be exempt from expedited reporting but will be documented on a study specific SAE form.

Unexpected SAE

An adverse event that meets the definition of serious and is not listed in the protocol or SmPC or the most recent informed consent document for the study.

Unexpected Adverse Reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable product information.

Source Data

Source data for this study will consist of medical and nursing case notes and the Royal Marsden Hospital Electronic Patient Record. The case report form (CRF) will not be defined as source data for the study.

Assessment of adverse events

Adverse events should be evaluated for seriousness, causality, severity and expectedness by the Chief Investigator or designee as follows:

A. Seriousness Assessment and Recording:

The event results in one of the following:

Any untoward medical occurrence or effect that at any dose that results in:

death

is life-threatening

requires hospitalisation or prolongation of existing hospitalisation

results in persistent or significant disability or incapacity

is a congenital anomaly or birth defect

is an important medical event

or has been identified within the protocol or reference document (e.g. SmPC) as an SAE.

Any members of research teams who observe an SAE are responsible for reporting SAEs to the CI within 24hrs of knowledge as illustrated in the flow chart below.

All SAEs have to be entered onto the study specific SAE form.

B. Causality Assessment:

All serious adverse events judged by either the Chief Investigator or designee or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as serious adverse reactions. The event should be assessed for their possible association to the study drug(s) and the decision should be classed as either definitely, probably, possibly, unlikely, or unrelated.

If there is a difference in opinion with regards to events grading between CI and designee, the highest grading will be used for reporting purposes.

Relationship	Description
Unrelated	There is no evidence of a possible causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event e.g. other concomitant medication.
Possibly	There is evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication. However, other factors may also be involved e.g. concomitant medications.
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship with the trial medication and the influence of other factors is unlikely.

C. Expectedness Assessment

Serious adverse reactions should be considered as <u>unexpected</u> if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information for the IMP.

The expectedness of an adverse reaction shall be determined according to the SmPC. If the event is not listed in the protocol or IB as an expected side-effect, then this is an unexpected serious adverse reaction in relation to the study drug(s).

If the nature of the event is consistent with the safety profile of the drug and is listed as an expected event in the appendix, then this is exempt from reporting as an SAE.

D. Severity Assessment

Severe is defined as an intensity classification (mild, moderate or severe). The severity of serious adverse events may also be graded according to NCI-CTCAE, version 3 or as stipulated in the protocol, where applicable. For each episode, the highest severity grade attained should be reported.

For events that are not listed in the CTCAE, the investigator should evaluate its severity using the table below.

Severity grade	Description
Mild	Grade 1 – Does not interfere with the patient's usual function (patient is aware of symptoms or signs but there are easily tolerated). Acceptable.
Moderate	Grade 2 – Interferes to some extent with the patient's usual function (enough discomfort to interfere with the patient's usual level). Disturbing.
Severe	Grade 3 – Interferes significantly with the patient's usual function (incapacity to work or do usual activities.) Unacceptable.
Life-threatening/disabling	Grade 4 – Results in risk of death, organ damage or permanent disability (unacceptable).
Death	Grade 5 – event has a fatal outcome.

Reporting Guidelines

The C.I must evaluate each adverse event and classify the event as an SAE, SAR or SUSAR and determine whether expedited reporting is required based on protocol or reference documents. The events should also be recorded in the CRF.

For events requiring expedited reporting, the responsibility of initial assessment and reporting to the MHRA, Novartis and the REC is delegated by RMH/ICR to the C.I.

Adverse Events

AEs that are not considered serious should be documented on the source documents or CRF.

Serious Adverse Events/Reactions

For adverse events/reactions that are regarded as serious, investigators are responsible for reporting to the C.I immediately or **within 24 hours of knowledge of the event** (except for those SAEs which have been listed as being exempt and therefore not requiring immediate reporting).

All SAEs should be followed up until resolution. Follow up reports for SAE/R should be submitted at appropriate intervals until resolution. All the information should be recorded on the SAE forms.

The C.I or designated individual should submit a follow up report within 8 calendar days. If additional information is unavailable (e.g. awaiting post-mortem results), then the authorities should be notified in writing to inform them of this and then additional information should be provided as soon as the information becomes available.

SUSARs

All unexpected SAEs and SUSARs must be reported to Novartis and to the R&D Office in accordance with the MHRA and main REC reporting requirements

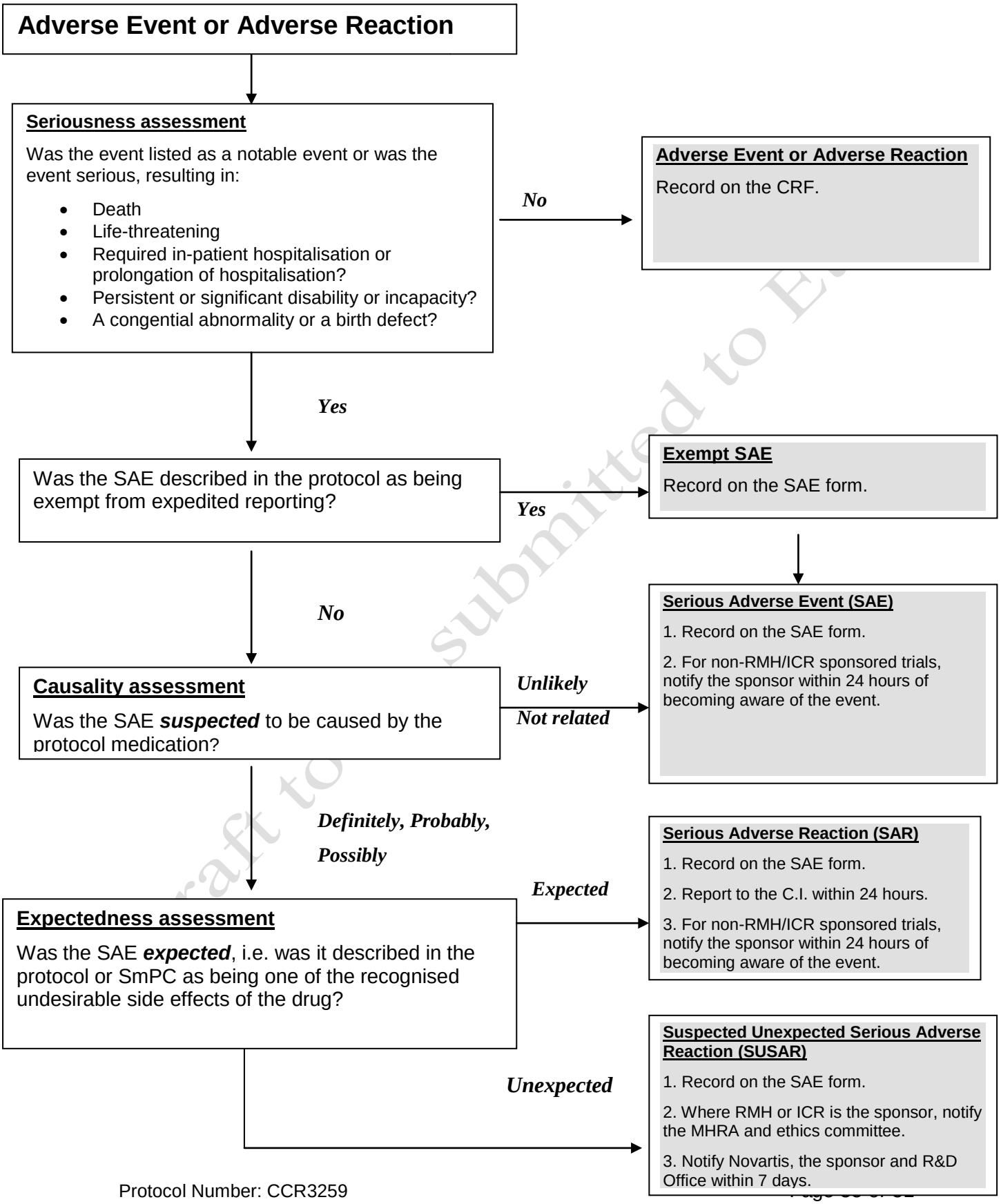
Observation period for adverse events

For the purpose of this trial, all adverse events/serious adverse events will be collected from the day of consenting to until 30 days after the last administration of the Investigational Medicinal Products.

Timeframe for reporting SAEs

Event	Reported by	Report to	Time
All SAEs –Initial Report **Follow-up reports**	Researchers/PI	Chief Investigator	**Within 24 hours** **ASAP**
All fatal or life-threatening SUSARs – Initial Report **Follow-up reports**	CI or nominated representative	Novartis, MHRA & Main REC & R&D Office	**Within 7 calendar days** **8 days**
All other SUSARs **Follow-up reports**	CI or nominated representative	Novartis, MHRA & Main REC & R&D Office	**Within 15 calendar days** **ASAP**
All SARs, suspected SARs, (SSARs) and SUSARs, with a summary of any issues affecting safety of participants.	CI or nominated representative	Novartis, MHRA & Main REC& R&D	**Annual Safety Report**

Assessment and Reporting of AEs, SAEs and SUSARs



Appendix C RECIST

For the purpose of this study definitions of tumour assessments will be based on Response Evaluation Criteria in Solid Tumours (RECIST)[26].

Evaluation of measurable and non-measurable lesions

1. Measurable disease – the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/ histology.
2. Measurable lesion – lesions that can be accurately measured in at least one dimension with the longest diameter $\geq$ 20 mm using conventional techniques or $\geq$ 10 mm, with a spiral CT scan.
3. Non-measurable lesions – all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or $\geq$ 10 mm, with a spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions and also abdominal masses that are not confirmed and followed by imaging techniques.
4. All measurements should be taken and recorded in metric notation, using a ruler or calipers. All screening evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.
5. The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow up.
6. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion is recommended.

Methods of measurement

1. CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.

2. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung, however CT scans are preferable.

3. When the primary endpoint of the study is objective response evaluation, ultrasound should not be used to measure tumour lesions. It is however a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound may also be used to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

4. The utilisation of endoscopy and laparoscopy for objective tumour evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may not be available in some centres. Therefore the utilisation of such techniques for objective tumour response should be restricted to validation purposes in specialised centres. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Baseline documentation of target and non-target lesions

1. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
2. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements.
3. A sum of the longest diameters (LD) for all target lesions will be calculated and reported as the baseline sum of LD. The baseline sum LD will be used as reference by which to characterise the objective tumour.
4. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow up.

Response criteria

Response criteria	**Evaluation of Target lesions**
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum of LD.
Progressive Disease (PD)	At least 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD)	Nether sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

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

* Although a clear progression of a non-target lesion is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is

objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

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

Appendix D Schedule of Events

Assessments	Screen	#1 d1	#2 d1	#2 d15	#2 d15-22	#2 d22	#3 d1	#4 d1	#odd	#even
Consent	X									
Demography/ History	X	X	X	X		X	X	X	X	X
Pregnancy Test	X &									
Physical Examination	X	X	X	X		X	X	X	X	X
Lab analysis (FBC, Coag, Biochemistry, glc, lipids, HbA1c)	X *	X	X	X		X	X	X	X	X
Lung function tests	X		X	X			Repeat if clinically indicated only			
Start everolimus		X	Everolimus to be stopped on #2 d15 and restarted when recovered from nephrectomy (= #3 d1)							
Staging CT	X *				X		X		X	
MR Functional imaging	X (pre-biopsy)				X		Repeat at PD			
Tumour biopsy	X						Re-biopsy PD			
Nephrectomy						X				
CTCs/CECs/Biomarkers		X	X	X		X	X	X	X	X and further sample at PD

& must be performed within 3 days of #1 d1

* must be performed within 7 days of #1 d1

1 cycle of treatment is defined as 28 days

#3 d1 is defined as the time point at which everolimus is restarted post-operatively

Appendix E Translational and functional imaging research studies

1 Introduction

The combined infrastructure and ongoing research within the CR-UK London Research Institute, and the Royal Marsden Hospital puts us in an unparalleled position to identify novel sensitivity pathways to mTOR inhibition in renal cancer.

A key aim of this study is to evaluate changes in circulating and tumour biomarkers in relation to tumour response guided by conventional and novel imaging techniques developed at the Royal Marsden Hospital. These biomarkers are developing from ongoing whole genome functional RNAi studies in renal cancer model systems and from synthetic lethal mTOR inhibitor and hypoxia RNAi screens conducted within the London Research Institute (LRI) in the laboratories of Charles Swanton and Julian Downward.

The expression of these putative biomarkers of renal cancer response will be evaluated in tumours before and after treatment and correlated with novel functional imaging techniques to define therapeutic response to treatment. In addition, novel techniques will be applied to patients with renal cancer to identify whether circulating tumour DNA, circulating microRNAs, endothelial cells and tumour cells can guide the identification of patients with disease sensitive to mTOR inhibition and provide insight into resistance mechanisms associated with everolimus treatment.

Analysis of tissue for such studies will be performed in the laboratories of Dr Charles Swanton, London Research Institute.

2 Tissue Acquisition and Processing

Acquisition and Processing of Tumour Tissue

A biopsy of the primary tumour will be performed prior to starting treatment and this sample will be analyzed in conjunction with the subsequent nephrectomy specimen**.** Five tissue cores from one needle puncture will be obtained; one will be sent for paraffin embedding and analysis by the pathologist to establish a histological diagnosis. The remaining cores will be snap frozen in liquid nitrogen within 30 minutes after biopsy and stored at -80°C. The biopsies will be transferred to the laboratory on dry ice in special sample containers. Two of the frozen biopsy samples will go to the laboratory of Charles Swanton, and the remainder will be available for further analysis in the future or in the event of problems with other cores. Core biopsies obtained at the time of tumour progression will be snap frozen and sent to the laboratory of Charles Swanton as described.

The nephrectomy specimen will be dissected by the pathologist to obtain sufficient material for routine diagnostic purposes. After that, separate samples from the tumour and from the remaining normal kidney tissue will be taken for translational research studies. These tissues will be snap frozen in liquid nitrogen within 1 hour after the blood supply to the kidney has been interrupted and stored at -80°C until transferred to the laboratory of Charles Swanton as described.

In addition, a fresh tumour tissue sample will be collected from large nephrectomy specimens and couriered immediately to Charles Swanton's laboratory in standard growth medium for the isolation of live tumour and stromal cells for primary culture and establishment of cell lines.

Microdissection of Snap Frozen Tumour Tissue

Processing of core biopsy and nephrectomy specimens will be conducted in the laboratory of Prof Gordon Stamp (Histopathology Core Technology Facility, London Research Institute). Microdissection of tumour samples will be performed to separate malignant cells from associated stromal components and RNA and DNA from each will be extracted immediately after dissection according to GLP standards.

Paraffin Embedded Tissue Sections

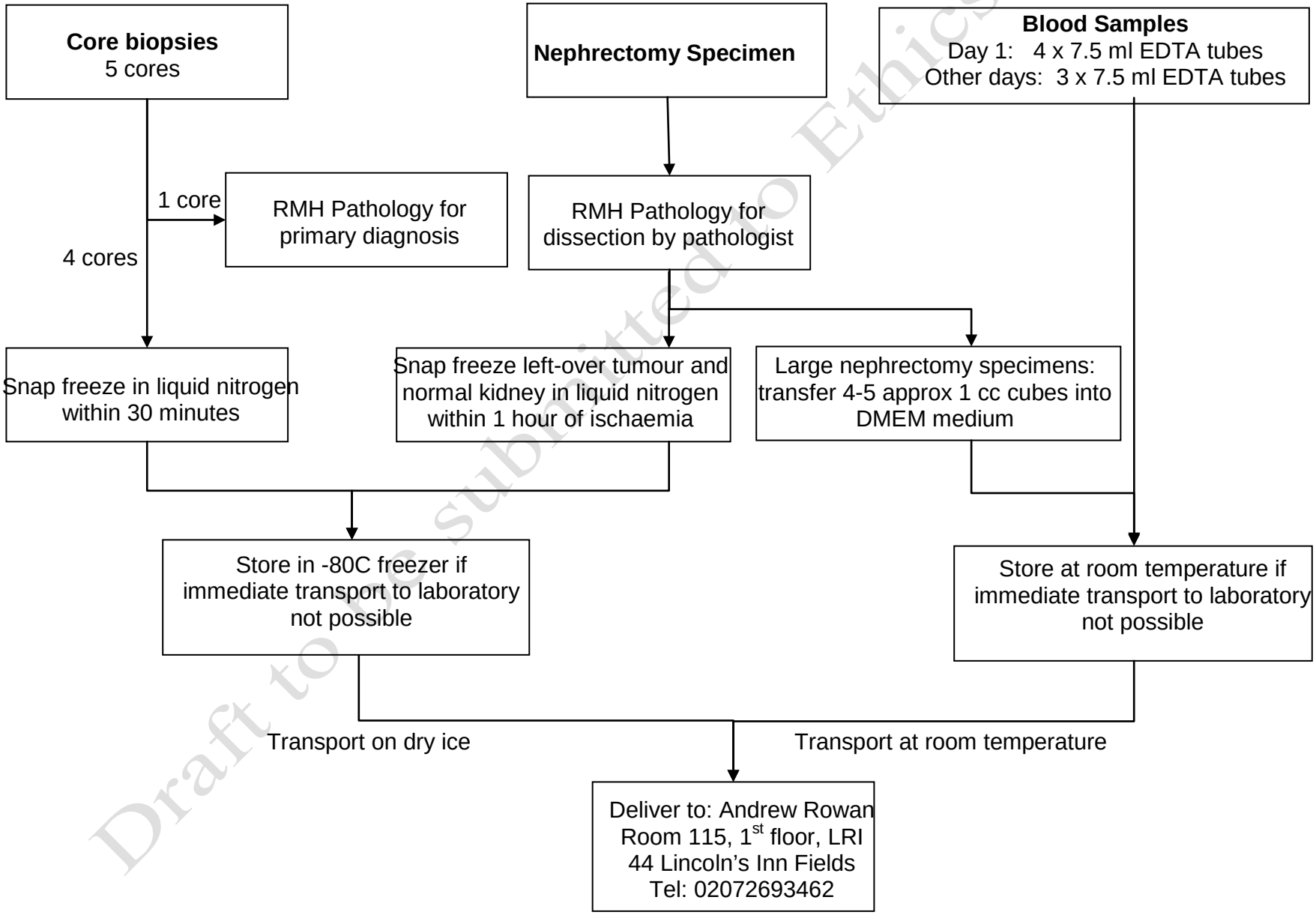
Paraffin embedded core biopsies and nephrectomy specimens that are no longer needed by the pathologist for diagnostic purposes will be cut in 5-10 μm sections and mounted on pathology slides for immunohistochemistry and in situ hybridization experiments. 10 slides of each specimen will be transferred to the laboratory of Charles Swanton. Tissue microarrays might be produced from individual pathology specimens to facilitate sample analysis and processed as described.

Blood Collection and Processing

Venous blood for biomarker analysis will be collected in 7.5ml EDTA tubes. Four tubes will be collected on day 1 prior to starting everolimus treatment and 3 tubes each will be taken on days 1 of cycle 2, day 15 of cycle 2, on day 22 of cycle 2 prior to nephrectomy and on the first day of all treatment cycles post-nephrectomy.

Blood samples will be taken and transported to the laboratory of Dr Swanton immediately for processing. One whole blood sample will be used for the detection and isolation of circulating tumour cells and endothelial cells on the same day. Two further samples will be centrifuged within 4 hours of collection to separate plasma and cellular particles which will be transferred to separate tubes and frozen at -80°C until used for nucleic acid and ELISA analysis. The fourth sample taken on day 1 will also be separated and stored at -80°C for future analysis.

Translational research specimens sample flow, storage conditions and contacts



Specimen labeling

Each specimen container will be labeled with the trial name, the anonymised patient identification number, the date and time when the sample was collected and the type of tissue or specimen contained. All samples will be catalogued in an electronic database in the laboratory of Charles Swanton. The time from core biopsy collection to snap freezing and from ischaemia to snap freezing for nephrectomy specimens will be recorded on the database. All tissues will be stored in an alarmed and locked -80°C freezer which is dedicated to the storage of clinical trial patient samples and located in the Basement 3 of the London Research Institute (freezer #49).

3 Analysis of tumour tissues

The specified techniques are based on the current literature. Equivalent novel methods and technologies might be used at the time of analysis.

RNA and miRNA Expression Analysis

Total RNA from renal specimens will be isolated from tissue obtained before and after everolimus exposure and at the time of tumour progression by the Ovation Pico Kit (NuGen, San Carlos, USA) which is specifically designed for the extraction of small RNA quantities. The effects of everolimus on changes in genome wide and targeted gene expression patterns in malignant cells and tumour stroma will be analyzed by RNA expression analysis with Exon Array 1.0 GeneChips (Affymetrix, Santa Clara, USA). The expression patterns of these tissues will be compared between responding patients, those who achieve disease stabilization and those who progress despite everolimus treatment. MicroRNA will be extracted from tissue homogenates with the mirVANA Paris kit (Ambion, Foster City, USA) and miRNAs expression patterns in malignant cells and possibly other tissues will be analyzed with the TaqMan® microRNA v2.0 Array System (Applied Biosystems, Foster City, CA).

Tumour DNA Sequence and Copy Number Analysis

Whole genome sequencing of tumour tissue DNA and RNA using Solexa deep sequencing technology (Illumina, San Diego, USA) will also be conducted. Sequencing will include but not be restricted to regulators of VEGFR, PI3K, mTOR, S6K and VHL pathways including novel regulators of mTOR/S6K pathway signaling identified from functional genomic datasets to identify candidate genes associated with resistance and sensitivity prior to and after everolimus treatment**.** Tumours will also be profiled for chromosomal numerical heterogeneity status by FISH and for gene copy number variations by Affymetrix SNP 6.0 arrays.

Tumour Immunohistochemistry and In Situ Hybridization

Molecular analyses of paraffin embedded tissue sections will be carried out to determine the effects of everolimus on changes in the phosphorylation status of proteins in the mTOR signaling pathway in tumour tissue (to include PTEN, p-AKT, p-PRAS40, p-70S6K, p-S6RP, p-4E-BP1) and to determine the effects of everolimus on changes in the levels of target genes and proteins in the VHL-HIF pathway in tumour tissue (to include VHL, HIF, VEGF family, GLUT-1). Additional pathways may be evaluated based on the contemporary literature at the time of analysis. The tumour vasculature will be analyzed in pre- and post everolimus-treatment tissues by endothelial marker staining and by collagen IV staining which identifies remnant extracellular

matrix scaffolds from degenerated blood vessels. These techniques will be used in conjunction with novel markers of neo-angiogenesis to study vascular remodeling in the laboratories of Holger Gerhardt and Charles Swanton at the London Research Institute.

Primary Culture of Malignant and Stromal Cells/In vivo model systems

Fresh tumour tissue will be processed immediately after transfer in culture medium to Charles Swanton's laboratory. The tissue will be mechanically dissected and grown in the primary cell culture facilities of the CR-UK London Research Institute. Malignant and stromal cells will be separated and analyzed in in-vitro angiogenesis and kidney cancer models to analyze the contribution of these different cellular compartments to the development of everolimus resistance. Cell lines will be established from cells that retain proliferative potential after an extended time of in vitro growth and model murine systems will be established subject to appropriate regulatory approval.

4 Analysis of Circulating Biomarkers to Predict Therapeutic Responses

The specified techniques are based on the current literature. Equivalent novel methods and technologies might be used at the time of analysis. This work may be performed outside of the publication timelines of the final Trial report.

Circulating Angiogenic Markers

Levels of the circulating factors VEGF, soluble VEGF-receptors (sVEGFR) and Placenta Growth Factor (PIGF) are influenced by treatment with antiangiogenic agents like sunitinib and pretreatment levels of some of these factors and changes with drug treatment have been shown to correlate with clinical outcome measures in kidney cancer patient. Plasma levels of VEGF, PIGF, sVEGFR1-3 and new regulators of angiogenesis will be measured by ELISA analysis of plasma samples collected immediately before starting everolimus and on treatment. High-throughput deep-proteome analysis will be used to identify new protein biomarkers that predict everolimus sensitivity and resistance. Circulating endothelial and progenitor cells will be quantified by FACS analysis of erythrocyte lysed whole blood samples. Levels of circulating markers at baseline and after everolimus treatment will be correlated with clinical, functional imaging and gene expression data.

Circulating Tumour Cell Analysis

Circulating tumour cells will be extracted from patient's blood by magnetic bead cell sorting using negative selection with anti-CD45 beads (Miltenyi Biotec, Bergisch Gladbach, Germany) to deplete leukocytes and subsequent positive selection by cytokeratin staining and FACS sorting. Alternatively, the CellSearch system (Veridex, Raritan, USA) might be used (depending on availability). Circulating tumour cell numbers will be correlated with therapeutic outcomes and the isolated tumour cells will be used for genetic expression and copy number analysis as described.

Analysis of Circulating MicroRNA

MicroRNAs (miRNAs) are small non-coding RNAs that negatively regulate gene expression through the inhibition of mRNA translation or the initiation of mRNA degradation. The tissue specific expression of miRNAs has provoked intense investigation to identify whether these non-

coding RNAs can reflect signatures of tumour origin, prognosis and outcome. If the association of miRNAs with prognosis can be shown to be directly causative, they may represent excellent therapeutic targets due to their potential ability to influence multiple biological processes by altering the expression and translation of many mRNAs. In this regard several miRNAs have now been attributed with direct roles in tumour invasion, tumour growth and motility and in the activation or repression of cancer survival signalling and angiogenic pathways. Furthermore, tumour derived circulating miRNAs have been identified in human blood [2] and may represent excellent biomarkers to identify patients who may be more likely to benefit from targeted agents. Total RNA from human blood will be isolated with the mirVANA Paris kit (Ambion, Foster City, CA) before and after everolimus exposure. RNA concentration will be quantified using NanoDrop Spectrophotometer (NanoDrop Technologies, USA). For analysis of differential miRNA expression we will use the TaqMan microRNA v2.0 Array System (Applied Biosystems, Foster City, CA). Results will be compared with miRNA expression in matched tumour samples and data analyzed in the Bioinformatics department at the London Research Institute.

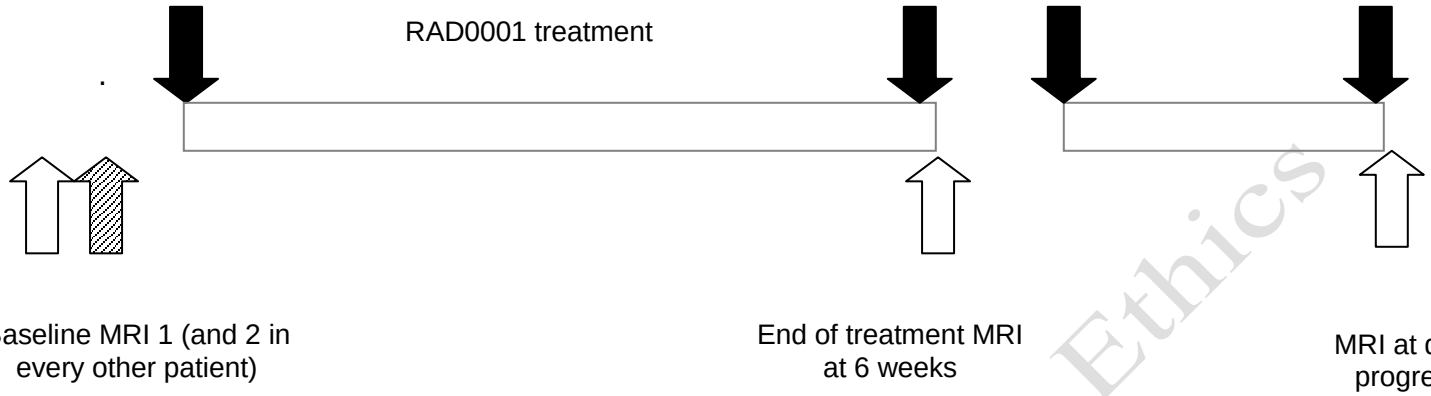
Analysis of Circulating Tumour DNA

Circulating tumour DNA will be quantified to analyze tumour dynamics during everolimus treatment. Circulating cell-free DNA will be isolated from plasma samples after double centrifugation to remove any cellular components and debris and the amount of circulating DNA of mutated genes that were identified in the tumour DNA sequencing project will be quantified by real time PCR analysis and BEAM as described [3] or by Solexa (Illumina, San Diego, USA) high throughput sequencing techniques.

Isolation of Genomic DNA from Peripheral Blood

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

5 Functional Magnetic Resonance Imaging



Rationale

There is evidence to suggest that the major mechanism of action of mTOR inhibition in renal cell cancer is related to its effect on angiogenesis. Inhibition of mTORC1 by temsirolimus has been shown to reduce the expression of HIF1α and HIF2α, which are potent drivers of VEGF and PDGF overexpression.. mTOR inhibition has been shown to reduce vascular sprouting, which is likely to result in measurable changes in quantitative vascular parameters derived using DCE-MRI studies.

Diffusion-weighted MR imaging (DW-MRI) allows the apparent diffusion coefficient (ADC) value of tumours to be calculated. Diffusion-weighted MR imaging can be used to probe cell death from apoptosis, necrosis and autophagy downstream to inhibition of angiogenesis. Cell death results in an increase in the ADC value. By performing DW-MRI using smaller diffusion-weighting or b-values, it is possible to estimate the micro-capillary perfusion within tumours, which is also anticipated to reduce as a result of mTOR therapy.

Objectives of functional imaging evaluation

DCE-MRI

Primary objectives

1. To determine whether a measurable change can be observed in the model-based quantitative vascular parameters derived using DCE-MRI before and after mTOR treatment.

Secondary objectives

2. To correlate changes observed in the model-based quantitative vascular parameters derived using DCE-MRI with other biomarkers of drug activity/ pathway inhibition and histopathology.

DW-MRI

Primary objectives

1. To determine whether ADC changes with RAD001 treatment in patients with renal cancer.

Secondary objectives

2. To validate ADC changes observed on DW-MRI imaging with histopathology.
3. To determine whether the pre-treatment ADC has any relationship with treatment effects (compared with other biochemical, cytological and histological features of response).

Patient inclusion and exclusion:

Inclusion criteria for imaging study:

1. Patient fulfil clinical criteria for RAD0001 treatment as per protocol
2. Lesion measuring at least 2 cm in maximum diameter

Exclusion criteria for imaging study:

1. Contraindications to MR imaging (e.g. pacemaker, aneurysmal clips, severe claustrophobia)
2. Severe renal impairment which contraindicates administration of contrast medium
3. History of allergy to gadolinium contrast medium
4. Severe patient dyspnoea such that they are unable to breath-hold for at least 10 seconds.
5. No peripheral vascular access

MR imaging evaluation

Patient preparation:

Patient should be well hydrated on the day of the MR imaging study. Fasting is not necessary prior to MR study. When the patient arrives at the MR unit, a 16G or larger venous cannula will be inserted into a vein within the antecubital fossa.

MR imaging technique

Conventional morphological imaging will be performed using T1 and T2-weighted axial and coronal images. Diffusion-weighted MR imaging will be performed using respiratory triggered or free-breathing single-shot echo-planar imaging technique using multiple b-values (between 0 and 900 s/mm^2). Prior to intravenous contrast administration, T1-calibration experiment will be performed by performing PD and T1-weighted imaging using variable flip angle technique. The arterial input function will be obtained from the supplying renal artery using a pre-bolus technique and performed using fast gradient-echo T1-weighted acquisition in the coronal plane. Coronal dynamic contrast enhanced MR imaging will be performed with dual volume acquisition in sequential breath-holds. The total MR examination should not exceed 45 minutes. The imaging acquisitions are summarized below:

1. Breath-hold T1-weighted gradient-echo (axial)
2. Respiratory triggered T2-weighted turbo spin-echo images (coronal)
3. Low flip angles T1-weighted gradient echo (coronal)
4. Quantitative T1-mapping
5. Pre-bolus T1-weighted gradient echo measurement (coronal)
6. Diffusion-weighted MR imaging using fat suppressed single-shot spin-echo echo-planar MR imaging technique (coronal), using b-values between 0 and 900 s/mm^2
7. Navigator-controlled dynamic contrast enhanced T1-weighted MR imaging (coronal)
8. Post contrast low flip angles T1-eighted gradient echo (coronal)
9. Post contrast T1-weighted VIBE (coronal)

Data analysis

Data will be analysed off-line using specialized software (MRIW, Institute of Cancer Research, UK; 3D-View, Biotronics, UK and DiffusioView, Institute of Cancer Research, UK).

For DCE-MRI data, model based analyss will be used to derive quantitative indices (transfer constant, *Ktrans*; extracellular volume, *Ve* and efflux constant, *Kep*). These parameters will be compared before and after RAD0001 treatment. It has been reported that mTOR inhibition was associated with early reduction in *Ktrans* and changes in the interstitial fluid pressure (IFP), and we hypothesise that the changes in IFP may be reflected by a change in the extracellular volume (*Ve*) measured using DCE-MRI.

DW_MRI using multiple b-values allows for the calculation of the ADC total, perfusion insensitive ADC (ADC high) and the perfusion-sensitive ADC (ADC low). These ADC indices will be compared before and after RAD0001 treatment.The quantitative indices derived using DCE-MRI an DW-MRI will be correlated with biochemical marker of VEGF expression, circulating microRNA and circulating tumour cells. Following surgery, radiological-pathological comparison will be made to compare the MR imaging derived functional imaging parameteric maps with gross pathology as well as with histological features of angiogenesis and cellular necrosis.

Statistical considerations

Based on prior DCE-MRI and DW-MRI studies, the measurement reproducibility of quantitative parameters derived on state or the art MR scanners is usually about 20 to 30%. Assuming that our technique is able to confidently detect a 30% or greater reduction in the efflux constant Ktrans, and that the log ratio of Ktrans before and after treatment is 0,40 (Standard deviation of Ktrans ratio before and after treatment are 0.35 and 0.49 respectively), a study population of 18 patients will have 80% power of detecting this difference ($\alpha = 0.05$).

Appendix F IB for Everolimus

A Summary of Product Characteristics (SmPC) will be used as a reference document for this trial. Novartis are responsible for providing a SmPC for the Clinical Trial Authorisation submission and upon approval of study, annual updates to SmPC to the Chief Investigator.