CLINICAL STUDY PROTOCOL CCR4232

A Phase 1, first in man, dual centre, open-label dose escalation study with expansion to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of CCT3833, a panRAF inhibitor, given orally in patients with advanced solid tumours, including metastatic melanoma.

Protocol Version :	5.1
Sponsor Protocol Number:	CCR4232
EudraCT Number:	2014-003988-38
Date:	25 March 2017
Chief Investigator:	Dr James Larkin Renal and Melanoma Unit The Royal Marsden NHS Foundation Trust 203 Fulham Road London SW3 6JJ Tel: 020 7811 8576 Fax: 020 7811 8103
Sponsor:	The Royal Marsden NHS Foundation Trust 203 Fulham Road London SW3 6JJ Tel: 020 8642 6011 x1327 Fax: 020 8915 6762 The Institute of Cancer Research Royal Cancer Hospital 123 Old Brompton Road London SW7 3RP Tel: 020 7352 8133 Fax: 020 7370 5261
Funding:	NIHR Royal Marsden and the Institute for Cancer Research Biomedical Research Centre The Royal Marsden NHS Foundation Trust Downs Road Sutton SM2 5NG

PROTOCOL SUMMARY

Protocol Number	CCR4232
Investigational Medicinal Product	CCT3833
Title	A Phase 1, first-in-man, dual-centre, open-label, dose escalation study with expansion to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of CCT3833, a panRAF inhibitor, given orally in patients with advanced solid tumours, including metastatic melanoma.
Phase	1/2
EudraCT	2014-003988-38
Study Objectives	To establish the safety and recommended Phase 2 dose of CCT3833 in patients with advanced solid tumours, and investigate its pharmacokinetic, early anti-tumour and pharmacodynamic activity, in an expanded cohort of clinically and molecularly defined melanoma patients.
Study Design	A multi-centre, open-label, dose escalation Phase 1 study, with a subsequent expansion phase.
Trial Population	Part A - Dose escalation stage: advanced solid tumours. Part B - Expansion cohorts: advanced melanoma.
Treatment Regimen	CCT3833 delivered orally, dosed continuously, starting at 20mg once daily. One treatment cycle is 28 days. Cohorts of 3-6 patients will receive escalating doses of CCT3833. The expansion cohort will be treated with the recommended Phase 2 dose.
Recruitment target	Approximately 69 patients may be recruited to the trial. Up to 42 patients will be recruited to the dose escalation phase in a rolling six design, with the final number dependent on the number of dose escalations required to reach dose-limiting toxicity (DLT). The dose expansion stage will recruit approximately 27 patients in total, in 3 cohorts**.**
Primary endpoint	Recommended Phase 2 dose of CCT3833; Preliminary characterisation of CCT3833's safety and tolerability in humans.
Secondary endpoint	Characterisation of pharmacokinetics of CCT3833 in humans. Evidence of disease response to CCT3833 on imaging/clinically. Correlation between PK study results and CCT3833 tolerability/efficacy
Exploratory endpoints	Magnitude and duration of effect on biomarkers in plasma/tumour tissue following CCT3833 administration.
Study timeline	Recruitment is expected to run for 30-36 months, with a further 12 months of subsequent follow-up for survival.

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PROTOCOL SIGNATURES

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK Clinical Trials Regulations, the guidelines of Good Clinical Practice (GCP) the Declaration of Helsinki (Appendix 2), the applicable regulations of the relevant NHS Trusts and the trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Chief Investigator	
Investigator's Name	Dr James Larkin
Signature	
Date	30 Mar 2017
Sponsor Signature (On behalf of Sponsor)	
Name	
Signature	
Date	

AMENDMENT HISTORY

PROTOCOL VERSION/DATE	REASON FOR AMENDMENT
V 1.1 22 JAN 2015	FIRST RELEASE
V2.0 30 APR 2015	EXTRA BIOMARKER SAMPLE TIME POINTS AND ADDITIONAL ANALYSIS
V3.0 9 NOV 2015	UPDATE TO CAPSULE STRENGTH INFORMATION TO INCLUDE 75MG CAPSULES
V4.0 6 MAY 2016	FOR PATIENTS THAT HAVE INTRAPATIENT DOSE ESCALATION COLLECT PHARMACOKINETIC SAMPLES AT THE INCREASED DOSE AND FULL RANGE OF BIOMARKER ANALYSIS EXTENDED TO ALL PATIENTS
V5.0 6 DEC 2016	PROVIDE ADDITIONAL PK/PD DATA, PERMISSION TO CONDUCT COHORT 7 DOSTING, REVISED PATIENT DIARIES
V5.1 25 MAR 2017	CHANGE OF PI AT CHRISTIE SITE – DR MATTHEW KREBS

KEY TRIAL CONTACTS

Chief Investigator	Dr James Larkin Melanoma Unit The Royal Marsden NHS Foundation Trust 203 Fulham Road London SW3 6JJ Email: james.larkin@rmh.nhs.uk Tel: 020 7811 8576 Fax: 020 7811 8103
Co-Sponsor	The Royal Marsden NHS Foundation Trust 203 Fulham Road London SW3 6JJ
Co-Sponsor	The Institute of Cancer Research Royal Cancer Hospital 123 Old Brompton Road London SW7 3RP
Clinical Trials Unit	The Royal Marsden NHS Foundation Trust RM-CTU Downs Road, Sutton Surrey SM2 5PT Email: panraf@rmh.nhs.uk Tel: 020 8642 6011 x 4297 Fax: 020 8915 6762
Statistician	Ann Petruckevitch The Royal Marsden NHS Foundation Trust Downs Road, Sutton Surrey SM2 5PT Email: ann.petruckevitch@rmh.nhs.uk Tel: 020 8642 6011 Fax: 020 8915 6762

Participating centers and Principal Investigators	
Part A: 1	Dr Udai Banerji Senior Lecturer and Consultant Royal Marsden Hospital/Institute of Cancer Research Drug Development Unit Royal Marsden Hospital Downs Road, Sutton Surrey SM2 5PT Email:udai.banerji@icr.ac.uk Tel: 020 8661 3984 Fax: 020 8661 3541
Part A: 2	Dr Matthew Krebs Clinical Senior Lecturer and Honorary Consultant The Christie Hospital Clinical Trials Unit Wilmslow Road Manchester M20 4BX Email: matthew.krebs@christie.nhs.uk Tel: 0161 918 7672 Fax: 0161 446 8342
Part B: 1	Dr James Larkin Consultant Royal Marsden Hospital Melanoma Unit Royal Marsden Hospital 203 Fulham Road London SW3 6JJ Email: james.larkin@rmh.nhs.uk Tel: 020 7811 8576 Fax: 020 8915 6762
Part B: 2	Dr Paul Lorigan Consultant The Christie Hospital Melanoma Unit Wilmslow Road Manchester, M20 4BX Email:paul.lorigan@christie.nhs.uk Tel: 0161 446 3472 Fax: 0 161 446 3299
Clinical Fellow	Dr Zohra Ali Royal Marsden Hospital Melanoma Unit Royal Marsden Hospital 203 Fulham Road London SW3 6JJ Tel: 020 7811 8576 Fax: 020 7811 8103 Email: Zohra.ali@icr.ac.uk
Laboratory contacts	

Pharmacodynamics and exploratory research	Professor Richard Marais Cancer Research UK Manchester Institute University of Manchester Wilmslow Road Withington Manchester M20 4BX Tel: 0161 446 3101 Fax:0161 918 7491 Email: richard.marais@cruk.manchester.ac.uk Professor Caroline Dive Clinical and Experimental Pharmacology Cancer Research UK Manchester Institute University of Manchester Wilmslow Road Manchester M20 4BX Tel: 0161 446 3036 Email: caroline.dive@cruk.manchester.ac.uk
Pharmacokinetics/Bioanalysis	Covance Laboratories Otley Road Harrogate HG3 1PY UK Dr Charlie Brindley KinetAssist Limited Larchwood, ShieldhillRoad Qouthquan Lanarkshire, ML12 6NA UK

DEFINITION OF TERMS AND ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
AUC	Area under the concentration curve: Area under the concentration vs time curve
BA	Bioavailability
BRAF	A signal transduction serine/threonine-specific protein kinase of the Raf kinase family
cfDNA	Circulating free deoxyribonucleic acid (DNA)
CDX	CTC-derived xenograft
CI	Chief Investigator
CL	Plasma clearance
Cmax	The maximum plasma concentration of the drug
CR	Complete response
eCRF	Electronic case report form
CRO	Contract research organisation
CT	Computed tomography
CTCAE v4.03	Common Terminology Criteria for Adverse Events Version 4.03
CTLA-4	Cytotoxic T-lymphocyte antigen 4
CTA	Clinical trials authorisation
CTC	Circulating tumour cell
Cyclin D1	A protein which regulates cyclin-dependent protein kinase activity in G1 of the cell cycle
DDU	Drug development unit
DLT	Dose-limiting toxicity
DSUR	Development safety update report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EP	Early progression
EU	European Union
GCP	Good Clinical Practice
GI	Gastro-intestinal
GP	General practitioner
HNSTD	Highest non-severely toxic dose
HPMC	Hydroxy-propyl-methyl-cellulose

IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IRB	Independent review board
IUD	Intrauterine device
IUS	Intrauterine system
Ki67	A nuclear antigen that detects cells in synthesis phase; predicts proliferative activity of tumours
LHRH	Luteinising hormone releasing hormone
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MAD	Maximum administered dose
MAPK	Mitogen activated protein kinase
MEK	MAPK kinase: a dual-specificity kinase that phosphorylates the tyrosine and threonine residues on ERKs 1 and 2 required for activation
MHRA	Medicines and Healthcare Products Regulatory Agency
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
NHS	National Health Service
NRES	National Research Ethics Service
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic
PDX	Patient derived xenograft
PK	Pharmacokinetic
PI	Principal Investigator
PIL	Participant/patient information leaflet
PR	Partial response
PrD	Progressive disease
PS	Performance status
QA	Quality assured

R&D	NHS Trust R&D Department
RAS	'Rat sarcoma': a superfamily of intracellular signalling proteins
REC	Research ethics committee
RECIST v1.1	Response Evaluation Criteria in Solid Tumours Version 1.1
RMH	Royal Marsden NHS Foundation Trust
RP2D	Recommended Phase 2 dose
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SAR	Serious adverse reaction
SD	Stable disease
SDV	Source data verification
SI	Sub-Investigator
SMPC	Summary of medicinal product characteristics
SOP	Standard operating procedure
SRC	Safety review committee
STD	Severely toxic dose
SUSAR	Suspected Unexpected Serious Adverse Reactions
$T_{1/2}$	Half life of drug in plasma
T_{max}	The time of maximum concentration of drug in plasma
TMF	Trial master file
UK	United Kingdom
USM	Urgent safety measures
V600E	Amino acid substitution at position 600 in BRAF, from a valine (V) to a glutamic acid (E)
V_d	Volume of distribution
V_{ss}	Volume of distribution at steady state

1 BACKGROUND AND RATIONALE

1.1 Background

Malignant melanoma is a cancer arising from melanocytes. These cells originate embryonically in the neural crest and migrate to the epidermis, meninges and ectodermal mucosa. It therefore follows that although the majority of melanomas are cutaneous in origin, other sites such as the eye, gastrointestinal and genitourinary tract can also be the primary focus.

In the UK, melanoma currently accounts for approximately 4% of cancer cases and 1.4% of cancer deaths[21]. Despite being less common than non-melanoma skin cancer, melanoma is responsible for three times as many deaths each year as all other skin malignancies combined.

In the UK, malignant melanoma is now reported to be the fifth most common cancer[21]. Unlike many other malignancies, the incidence continues to rise on a yearly basis at a rate of 5-7%[7, 14]; this rising incidence is a global phenomenon, with the rate of increase being higher than for any other malignancy. Age demographics for the disease are unusual, with approximately 27% of new cases diagnosed in patients less than 50 years of age[21]. Melanoma is the most common malignancy in the 25-29 year age group. Melanoma therefore remains a malignancy of increasing epidemiological significance.

Whilst early detection of localised disease allows complete surgical resection and a potential cure, the historical lack of effective treatment options for advanced (metastatic) disease means that metastatic malignant melanoma accounts for a significant number of lives lost to a cancer. Median survival is in the region of 6-9 months[3, 35]. Given the young patient population affected, this represents a significant burden of potential life years lost.

1.1.1 Treatment of melanoma

1.1.1.1 *Melanoma treatment: chemotherapy*

Historically, conventional cytotoxic chemotherapy failed to impact significantly on the poor survival outcomes for patients with metastatic disease. Phase 3 trials[2, 5, 11, 26] using dacarbazine revealed a mere 10-20% response rate, with no impact on overall survival. Trials with other chemotherapeutic agents failed to demonstrate any advantage over dacarbazine; thus despite its poor anti-cancer activity in the majority of patients, its overall tolerability and the lack of an alternative enabled dacarbazine to become the standard therapy for melanoma.

1.1.1.2 *Melanoma treatment: immunotherapy*

Over recent years however, there have been marked changes in the melanoma treatment landscape, with developments in both immunotherapy and therapies targeting specific mutations. The discovery of CTLA-4, a T cell co-receptor, and the subsequent recognition that it provides a negative (down-regulatory) T cell signal,

translated into the development of the CTLA-4 targeted monoclonal antibody, Ipilimumab. In Phase 3 clinical trials[20, 31], this inhibitory antibody has demonstrated significant clinical efficacy, with a response rate of 10.9%, in both treatment naïve and pre-treated patients with metastatic melanoma. It is now approved in the EU for use in adults with advanced melanoma who have received prior therapy.

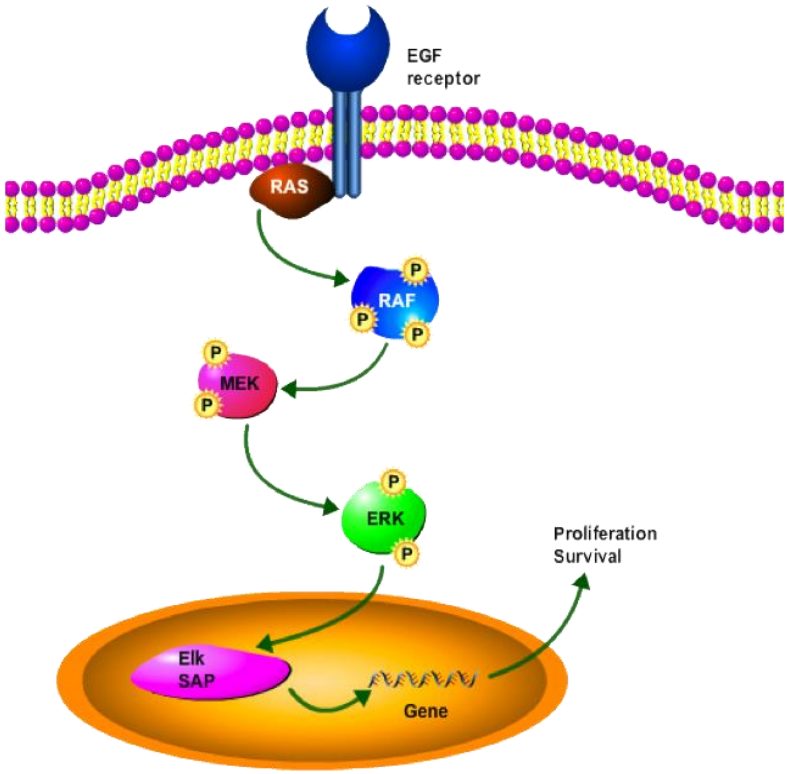
Another immune-modulatory strategy is that of anti-PD-1 and anti-PD-L1 antibodies. By impairing the interaction of the inhibitory receptor PD-1 on T cells with PD-L1 on tumour cells, these antibodies potentiate a tumour-specific T cell-mediated anti-tumour response. Although these agents remain in clinical trial, early results have been very encouraging[34, 39, 42].

1.1.1.3 *Melanoma treatment: targeted therapy*

The improved understanding of cancer cell biology has also led to the identification of specific genetic aberrations implicated in melanoma pathogenesis. Such knowledge has allowed the development of specifically targeted therapies shown to be efficacious in the clinical setting.

The mitogen activated protein kinase (MAPK) signal transduction pathway is crucial for growth, proliferation, differentiation and survival of cells. The pathway is strongly associated with human cancers[9, 15, 32, 38, 40], with approximately 50% of melanoma cell lines demonstrating a mutation in the BRAF gene and approximately 25% of melanomas bearing a RAS mutation. RAS mutation is the most common activating mutation in malignancies, present in approximately 15% of all human cancers. In melanoma[8, 40], the majority of mutations in BRAF are a substitution of glutamate for valine at codon 600 (V600E); a mutation that results in constitutive activation of the BRAF protein, causing unregulated signalling through the MAPK pathway, thus driving cancer growth and cell survival. Figure 1 is a schematic of the MAPK/ERK pathway.

Figure 1 Schematic of the MAPK/ERK pathway



The identification of BRAF as an appropriate therapeutic target was quickly followed with the development of effective BRAF targeted therapies for metastatic melanoma patients[13]. The Phase 3 clinical trial of vemurafenib[6], the first such targeted therapy, demonstrated a significantly improved progression free benefit relative to dacarbazine. Subsequent data[25, 33] has also confirmed an overall survival benefit with vemurafenib treatment, which is now approved in the EU for monotherapy treatment of adult patients with BRAF V600E mutation positive unresectable or metastatic melanoma.

Dabrafenib[1, 10, 23], another BRAF inhibitor with similar efficacy to vemurafenib, was also approved in 2013 in the EU, for a similar indication: 'treatment of adult patients with unresectable or metastatic melanoma with BRAF V600 mutation.'

1.1.1.4 *BRAF targeted therapy limitations*

Whilst the development of mutant BRAF targeted therapy has been a significant breakthrough in the management of metastatic melanoma patients, there remain a significant proportion of patients who relapse on the existing mutant BRAF treatments, or who have a mutant RAS gene. The most recent therapies vemurafenib and dabrafenib, are selective only for mutant BRAF-driving mutations and are not indicated for use in the latter group.

A proportion of patients will harbour a mutation in the RAS component of the MAPK pathway[4] instead of BRAF. In melanoma, up to 25% of tumours will carry a mutation in NRAS (although mutations in other RAS isoforms do exist). It has been demonstrated that BRAF inhibition by selective mutant BRAF inhibitors, in the presence of mutated RAS, results in pathway hyperactivation rather than inhibition, possibly potentiating tumour growth[18, 19]. The mutated-RAS driven mechanism is implicated in the development of some of the cutaneous side effects (keratoacanthomas and squamous cell carcinomas), occurring in approximately one third of patients on BRAF-targeted therapy. It has inspired further trials[12, 17,] using a combination of therapies targeted at different pathway protagonists, to prevent this paradoxical pathway activation and to reduce these cutaneous side effects.

An additional concern for selective BRAF targeted therapies is the development of drug resistance. Mutant BRAF melanoma patients respond rapidly and dramatically to BRAF inhibitor therapy. However, the response is short lived, with resistance emerging within a matter of months. The potential mechanisms[28, 37, 41] through which resistance develops are diverse, but include RAS mutations or upregulation[28], amplification or aberrant splicing of BRAF[29, 30] or CRAF[27], upregulation of COT[22] and overexpression of receptor tyrosine kinases (RTK)[19, 27, 29].

This ability of cancer to evolve and overcome even targeted therapies, makes it likely that a combinatorial or sequential therapeutic approach will be necessary to further improve survival outcomes in metastatic melanoma[24, 36]. Combination mutant BRAF and MEK targeted therapies are being investigated[12] as a strategy to circumvent development of drug resistance; further trials are also necessary to clarify the optimal sequence in which to use existing targeted and/or immunotherapies. Given the number of on-going trials investigating these issues, it is clear that melanoma treatment algorithms will continue to evolve rapidly over coming years. As new drugs are developed, it will be of increasing importance to establish where they will offer the most therapeutic benefit, be that in the primary treatment of newly diagnosed metastatic patients, or as a rescue therapy following progression on already established therapies. It is therefore important that there should be on-going development of new therapies, as well as on-going evaluation of the optimal sequence of administration of these new therapies, in malignant melanoma.

1.1.1.5 *Melanoma treatment: panRAF targeting*

As previously described, the MAPK pathway is strongly implicated in the pathogenesis of melanoma. The RAF kinases (BRAF and CRAF) are immediate downstream effectors of RAS, with CRAF described as the most important for mediating oncogenic RAS signalling. Unlike BRAF, CRAF is rarely mutated in human cancers and whilst BRAF only targets MEK as its substrate, CRAF is also thought to target other pathway components downstream of MEK.

Existing RAF inhibitors have selective anti-mutant BRAF activity, i.e. in tumour cells harbouring the BRAF mutation they effectively block BRAF activity, terminating pathway signalling. In BRAF wild type cells, or in cells where aberrant signalling is mediated by oncogenic RAS, the use of selective BRAF inhibition promotes MAPK signalling rather than inhibiting it[16]. Several theories exist regarding the mechanism for this, but all essentially describe the formation of heterodimers between BRAF and CRAF, the consequent transactivation of CRAF, and promotion of MAPK pathway signalling. Inhibitors effective against BRAF and CRAF ensure that both RAF isoforms are equally inhibited, preventing transactivation and thus terminating MAPK pathway signalling. This means that not only are mutant BRAF driven cancers inhibited, but additionally that mutant RAS-driven malignancies can also be treated, without the development of skin toxicities seen previously with selective RAF inhibitors. A panel of panRAF inhibitors has been developed by the ICR to exploit these observations for therapeutic gain; this trial aims to assess the safety and tolerability of the most promising of these inhibitors, CCT3833, in humans.

1.1.2 CCT3833 background

The package of non-clinical data summarised in the IB confirms that CCT3833 is a BRAF and CRAF inhibitor. There are licensed examples of BRAF inhibitors, and as such the mechanism of action is not entirely novel, but CCT3833 is a panRAF inhibitor which displays different activity from the licenced BRAF inhibitors. The package of *in vivo* and *in vitro* safety pharmacology data showed no evidence of significant safety signals in animals at likely therapeutic doses.

The therapeutic efficacy of CCT3833 was demonstrated *in vivo* and confirmed in a range of human tumour xenografts in mice at exposures that are anticipated to be achievable and tolerated in humans. Preliminary pharmacokinetic (PK)/pharmacodynamic (PD) relationships have been calculated based on limited data from the mouse and using PK/PD modelling methodologies.

The toxicological profile of CCT3833 was evaluated up to 28 days in GLP studies in rat and dog, and although No Observable Effect Levels (NOELs) were not identified in all studies the Severely Toxic Dose (STD) and Highest Non-Severely Toxic Dose (HNSTD) levels were identified in dog and rat, which were used in combination with human PK predictions to calculate a safe starting dose for human trials.

Microscopic pathology of 4-week study terminal kill rats and dogs showed some similarly affected organs/tissues, in muscle (minimal or slight inflammatory cell foci/myofibre degeneration), and gastrointestinal tract (stomach - minimal hyperkeratosis; duodenum - crypt microabscesses; colon & caecum - slight inflammatory cell infiltrate/mucosal basophilia; rectum - ulcers and myositis). Additionally, dogs showed increased inflammatory cell foci in liver, kidney, heart and brain, and haematopoiesis in spleen, femur and sternum. The generalised inflammatory changes were usually not more than minimal or slight, and were reflected in the clinical

pathology changes seen in dogs and rats and were generally reversible after 2 weeks with the exception of the inflammatory cell foci in the brain and kidney. Changes in haematopoietic tissues in dogs were also reflected in the changes in red blood cell parameters in life.

In both the rat and dog 4-week studies, where parameters were affected in the intermediate and/or low dose level as well as at the high dose, there were clear indications of dose relationship, with severity and/or incidence of findings increasing with increasing dose level.

These effects are considered to be monitorable in the clinic and they were shown to be generally reversible in both species. Clinical studies, which will be in those with advanced cancer, will include assessments of any haematological or muscle effects.

A starting dose of 20 mg CCT3833 per day is recommended as a safe initial dose for the first clinical study. This dose is predicted to produce peak plasma levels in humans below those seen at the STD/HNSTD in rat and dog, and is estimated to provide plasma exposure (AUC) safety margins between 1 and 16, depending on whether the PK in humans is closer to the rat or the dog. Based on mouse efficacy data and PK modelling, the proposed human starting dose is likely to generate circulating levels predicted to have pharmacological activity.

1.2 Study rationale

1.2.1 Rationale for study design

This is an open-label, multi-centre dose escalation (Part A) and dose expansion (Part B) study of CCT3833, administered orally to patients with advanced solid malignancies, including melanoma. The study design allows an escalation of dose with intensive safety monitoring to ensure the safety of patients. In Part A patients will be recruited as part of a rolling six design.

This study is designed such that in Part A, for the first cycle for each cohort, patients are given a single dose of CCT3833, followed by at least a 48-hour washout period, then continual once-daily dosing. Inclusion of this single dose and interval prior to multiple dose administration will permit assessment of single dose safety and will allow characterisation of both single and continuous dose PK and PD effects of CCT3833. For the first cohort, the starting dose will be 20 mg per day.

Part B will dose additional melanoma patients in 28-day cycles at the maximum tolerated dose (MTD), or at lower doses shown to be biologically active, safe and tolerable in Part A, in order to further explore tolerability and PK/PD effects, and to provide preliminary efficacy information.

There is currently no clinical experience with CCT3833. However, based on the preclinical safety and toxicology studies, a careful safety evaluation package has been

put in place to minimise the potential risk to patients and to discover potential toxicities in a timely manner.

Careful consideration has been given to the MHRA guidelines regarding the mitigation of risk in first-in-human clinical trials (see section 11.3.6); with regard to the mode of action, the nature of the target, and relevance to animal models, CCT3833 is regarded as low risk. CCT3833 does not meet the risk criteria defined by the UK MHRA Expert Advisory Group (EAG).

1.2.2 Rationale for study population

Melanoma can no longer be simply classified pathologically and treated as a single disease entity. Instead, the presence (or absence) of specific gene mutations results in disease categorisation into subgroups, each of which require different management strategies. It is this knowledge that prompted the decision to recruit patients into 3 distinct patient cohorts, based on their mutation and prior-treatment statuses, during the dose expansion stage of this trial. This will allow for the safety and tolerability of this panRAF inhibitor to be more closely investigated for each of these different clinical and molecular scenarios.

The first cohort proposed, melanoma patients who harbour the V600E mutation and have not previously been treated with a BRAF inhibitor, describes a significant majority of patients with newly diagnosed metastatic melanoma, and patients in whom disease has become locally advanced and thus no longer amenable to surgical resection. Current standard therapy for such patients is selective BRAF-targeted therapy (such as vemurafenib), however, evidence to date demonstrates (as previously mentioned) that even with such targeted therapy, disease progression commonly occurs (at latest) after a period of several months.

Although the treatment options available to BRAF-mutant melanoma patients have improved dramatically over recent years, the optimal sequence and/or combination of therapies is not yet known. This knowledge will evolve over the coming years as clinical experience with these agents increases. Including this cohort in the dose expansion stage of this trial will help determine whether more comprehensive panRAF blockade (rather than selective BRAF inhibition) could be safe and tolerable as a primary therapy against metastatic melanoma. If demonstrated, this would encourage further exploration of this as a treatment option for such patients. In order to avoid compromising patient care with an experimental therapy, rescue medication with a drug already approved for this indication (such as vemurafenib or dabrafenib) will be offered to patients who progress or withdraw from the study.

The second cohort proposed, melanoma patients who harbour the V600E mutation and have progressed on BRAF inhibitor therapy, represent an increasing population of patients who have previously benefited from targeted BRAF inhibition, but whose disease is now resistant to such therapy. The mechanisms of resistance to existing BRAF inhibitors (as previously mentioned) are complex and not fully understood, but are

thought, at least in part, to culminate in 'escape' reactivation of signalling through the MAPK pathway. Treatment options for such a resistant disease are currently limited. panRAF blockade may be effective in overcoming such drug resistance, due to the broader spectrum of panRAF inhibition; including this cohort of patients within the expansion stage of the trial will allow this potential to be investigated clinically.

The third patient cohort proposed, melanoma patients who harbour a RAS mutation, represent a population of patients for whom current BRAF-targeted therapy is not indicated and can in fact, as previously described, be deleterious. These patients are underserved by currently available targeted therapies, although they can benefit from immunotherapies. RAS mutant melanoma management remains an area of significant and on-going unmet clinical need. It is hypothesised that panRAF blockade will terminate the upstream enhanced signalling effect (via RAF) of mutated RAS, and thus inclusion of this cohort will allow further evaluation of panRAF inhibition as a safe and tolerable treatment strategy in this melanoma subpopulation.

1.2.3 Rationale for starting dose and regimen selection

A two-compartment model was considered to best represent the plasma concentration-time profiles of CCT3833 following single intravenous administration to mice, rats and dogs. Modelled plasma clearance (CL) of CCT3833 was 18.1, 11.4 and 60.4 mL/h/kg in mice, rats and dogs, respectively. The apparent volume of distribution at steady state (V_{ss}) of CCT3833 was 69.6, 59.6 and 238 mL/kg in mice, rats and dogs, respectively. Values of CL and V_{ss} in dogs were greater than expected based on bodyweight in comparison with rodents. Simple allometric scaling based on rodents predicted a human CL and V_{ss} of 285 mL/h and 2.96 L, respectively; data driven-allometry based on dogs gave predicted human values of 1733 mL/h and 9.68 L, respectively (see Table 1).

Table 1: Cross-species comparison of PK modelling data

Species	Modelled BA %	Modelled CL (mL/h)	Modelled V_d (L)	Modelled $t_{1/2}$
Mouse	43.5	18.1	69.6	2.8
Rat	NC	11.4	59.6	3.4
Dog	34.5	60.4	238	3.0
Human (predicted)	40	285*	2.96*	7.2*
		1733**	9.68**	3.89**

NC = not calculated; BA = bioavailability; CL = plasma clearance; V_d = volume of distribution; V_{ss} = V_d at steady state; $t_{1/2}$ = half-life.
* = based on rodent data
** = based on dog data

Oral bioavailability (BA) in rats (6 to 11 %) was markedly lower than that in mice (49%) and dogs (34 to 41%). The input (absorption) half-life after oral dosing in mice and dogs, estimated by deconvolution, was 1.22 and 1.16 h, respectively; oral BA was estimated to be 43.5 and 34.7 %, respectively (Table 1).

The maximum plasma concentration of the drug (C_{max}) and AUC values predicted for humans after a 20 mg oral dose of CCT3833 were 1900 ng/mL and 28100 ng.h/mL, respectively, based on rodents, and 436 ng/mL and 3180 ng.h/mL, respectively, based on dogs (see Table 2).

Table 2: Prediction of human exposures based on rodent and dogs

Dose to human	C_{max} (ng/mL)	AUC (ng.h/mL)	Species used for allometry
20 mg	1900	28100	rat, mouse
	436	3180	dog

The exposure predicted using the rodent data is the maximum likely in humans – that is, is it the most conservative prediction in terms of safety, since it gives the higher predicted exposure in humans. The exposure predicted from dogs may represent the potential lower range of exposure in humans.

A table comparing the predicted human exposures with exposures at the STD (rat) and HNSTD (dog) is given below (Table 3). Due to the similarity of male and female dog exposures at the HNSTD, margins are calculated on means of males and females. Since the male rat at 20 mg/kg was deemed to be at the STD, male rat exposure data alone was used for margins generation; male exposure was lower than female at 15 mg/kg and this is therefore the most conservative approach.

Table 3: Exposure margins for predicted human exposure compared with rat and dog safety study exposure

		C_{max} (ng/mL)	AUC (ng.h/mL)
20 mg dose to human	Predicted human value based on rodent PK	1900	28100
	Value at rat STD (margin)	12300 (x 6.5)	51000 (x 1.8)
	Value at dog HNSTD (margin)	5900 (x 3.1)	26700 (x 1.0)
	Predicted human value based on dog PK	436	3180
	Value at rat STD (margin)	12300 (x 28)	51000 (x 16)
	Value at dog HNSTD (margin)	5900 (x 14)	26700 (x 8.4)

The *in vivo* experiments performed to date have led to the decision that a once daily dosing schedule of CCT3833 will be investigated in this trial. One cycle will consist of 28 days. Alternative dosing schedules, such as twice daily, may also be investigated if the evolving data during the dose escalation stage suggests this may be appropriate.

1.2.4 Rationale for dose escalation increments

The assessment of PK/PD and its relationship to starting dose must be viewed in context of the fact that the efficacy model in mouse was the only *in vivo* PD model which contributed to the PK/PD analysis. In addition, the prediction of human PK covered a

wide range of exposures, depending on whether rodent or dog was used as the basis for extrapolation.

The efficacy model in mouse did yield plasma and tumour concentrations of CCT3833 at steady state PK, which gave quite consistent plasma/tumour concentration ratios. This allowed an estimation of the plasma concentrations at which efficacy might be expected to occur. The PK/PD model used generated an IC_{50} value for plasma vs tumour shrinkage, but the bottom part of the concentration-effect curve was not particularly well defined. The plasma IC_{50} value was 11.5 µM, or 6110 ng/mL.

The human PK predictions based on rodent data are very likely to represent the maximum exposures obtainable with any particular dose. The predicted clearance is exceptionally low, and the volume of distribution is essentially the lowest it could be (drug confined to the plasma compartment). The predicted exposures based on dog data are much lower, and actual human exposure is likely to lie within these two estimates.

When using the rodent-based prediction, i.e. predicting high human exposure for a given dose, a dose of 20 mg to humans would result in peak plasma levels lower than those observed at the corresponding STD/HNSTD dose levels in animal toxicology studies. A starting dose of 20 mg would thus, if based on rodent predictions, achieve high exposures in the first cohort, whilst not exceeding toxicology exposure margins. The peak plasma concentrations would be approximately one-third of the calculated plasma IC_{50} value in mice and therefore might reasonably be expected to demonstrate pharmacological activity.

If based on dog predictions, a dose of 20 mg would not achieve such high circulating concentrations, but plasma levels would still be predicted to have some pharmacological activity based on activity in mutant BRAF cell lines.

A starting dose of 20 mg CCT3833 is recommended as a safe initial starting dose for the FIM dose escalation study, Part A. This dose is predicted to produce peak human plasma levels below those at the STB/HNSTD in rat and dog, and is estimated to provide AUC safety margins between 1 and 16, depending whether the human PK is closer to the rodent or dog. It is also predicted to have pharmacological activity based on PK/PD assessment.

When the first single dose of 20 mg has been administered, the PK samples will be analysed to determine if human PK exposure falls within the expected range based on PK data from the dog, rodent, or neither. The decision to dose escalate will be determined by the human toxicology, e.g., dose doubling until grade 3 drug-related toxicity (or grade 4 haematological) of clinical relevance is encountered, as much as the rodent and non-rodent safety ratios. It is likely that the STD may be exceeded if escalations proceed as predicted (100% increments, i.e. doubling of the dose), but that

will only occur when the safety and tolerability and PK exposure data has been reviewed for the preceding dose level by the Safety Review Committee (SRC).

1.2.5 Rationale for expected toxicities and their management

The formal 4-week toxicity studies provided the most reliable assessment of the toxicological profile of CCT3833. In those studies, dogs were more profoundly affected in life than rats, with clear effects seen in both species. In dogs, routine clinical pathology monitoring revealed reductions in red blood cell-related parameters, increases in white blood cell-related measures, and increases in transaminases. Rats also showed white blood cell-related increases in the 4week study. In the 4week study, the single 4-week study, high dose rat with the most marked pathology in its group also showed some similar clinical pathology changes to those observed in the dog. In both species, clinical pathology changes showed partial or complete recovery following a treatment-free period.

In the 4-week rat study, there were no premature decedents. The most markedly affected high-dose (20mg/kg/day) terminal-kill rat (a male), in terms of pathology, showed more extensive inflammatory change than any other animal on study; together with a marked increased haemopoiesis in femur and sternum, minimal adrenal cortical vacuolation, marked thymic lymphocytolysis and moderate cardiomyopathy. The heart, adrenal and thymus changes were considered by the study pathologist to be secondary to generalised stress.

In the dog 4-week study, there was one decedent at the high-dose (25 mg/kg/day) level, and the dosing of remaining high-dose males was terminated on humane grounds. The decedent dog had enteritis in the ileum, lymphoid atrophy, and minor inflammatory cell foci/myofibre degeneration in the quadriceps muscle.

Microscopic pathology of 4-week study terminal-kill rats and dogs showed some similarly-affected organs/tissues, in muscle (minimal or slight inflammatory cell foci/myofibre degeneration), and gastrointestinal tract (stomach - minimal hyperkeratosis; duodenum - crypt microabscesses; colon & caecum - slight inflammatory cell infiltrate/mucosal basophilia; rectum - ulcers and myositis). Additionally, dogs showed increased inflammatory cell foci in liver, kidney, heart and brain, and haematopoiesis in spleen and femur.

The generalised inflammatory changes were usually not more than minimal or slight, were reflected in the clinical pathology changes seen in dogs and rats, and were generally reversible after 2 weeks, with the exception of the inflammatory cell foci in the brain and kidney. Changes in haematopoietic tissues in dogs were also reflected in the changes in red blood cell parameters in life. In both the rat and dog 4-week studies, where parameters were affected at the intermediate- and/or low-dose levels as well as at the high doses, there were clear indications of dose-related relationship between severity and/or incidence of findings and increasing dose level.

Routine clinical monitoring should provide early indications of tolerance in patient studies. The clinical laboratory tests will routinely include haematological parameters and assays for generalized inflammation. Given the consistent occurrence of slight muscle myofibre degeneration in both non-clinical species, specific markers for muscle degeneration/necrosis (such as creatinine, creatine kinase) will be included in clinical monitoring.

With regards to the potential for CCT3833 to show cardiovascular toxicity, the programme of non-clinical work undertaken on CCT3833 reflects its anticipated use as an anti-cancer agent, with an *in vitro* hERG study being the only stand-alone safety pharmacology work conducted. For *in vivo* work, safety pharmacology endpoints were incorporated in the pivotal rat and dog toxicity studies. From the programme undertaken, there were no consistent indications of cardiovascular effects associated with CCT3833; a small number of individual findings were observed. However, the effects associated with this class of compound in the clinic gives greater importance to these individual findings.

The hERG study showed no inhibition of cell tail currents, and there were no consistent effects in any of the ECG readings in the 4-week dog study. Similarly, there were no consistent patterns of marked changes in other cardiovascular measures, in either the rat or dog 4-week studies. In the dose-range-finding work in either species, there were also no indications of cardiovascular effects, although it should be borne in mind that the design of these studies did not include detailed cardiovascular investigations.

In the rat 4-week study, the one high-dose male rat that was more markedly affected than any other animal showed moderate cardiomyopathy, characterised by myocyte degeneration and infiltration of mononuclear inflammatory cells. The pattern of other histopathological findings in this animal led the study pathologist to conclude that the findings were secondary to generalised stress and not due to direct toxicity of CCT3833. Cardiomyopathy is occasionally recorded as a spontaneous non-treatment related finding in the rat.

In the dog 4-week study, there were minimal or slight inflammatory cell foci in the hearts of one or two low- and intermediate-dose male and two high-dose female main-study animals; after 2 weeks off-dose, one intermediate-dose female had slight inflammatory foci. In one of the high-dose main-study females with inflammatory cell foci, there was slight focal myocardial degeneration in the right atrium of the heart.

Overall, there was no strong evidence from the programme of preclinical safety studies for any dose-related effects of note on the cardiovascular system. However, public domain information on the cardiovascular effects of related products suggests that greater emphasis than normal should be placed on the individual and otherwise apparently unconnected, cardiovascular events which occurred in non-clinical safety testing with CCT3833.

In order to minimise any risks of cardiovascular toxicity, the proposed first-in-human trial protocol will exclude patients with any of the following:

- Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
  a. History or presence of ventricular tachyarrhythmia
  b. Presence of unstable atrial fibrillation (ventricular response >100bpm); patients with stable atrial fibrillation are eligible, provided they do not meet any of the other cardiac exclusion criteria
  c. Repeated presence of a prolonged QT interval >450ms at baseline (as calculated by Fridericia method)
  d. Unstable angina pectoris or acute myocardial infarction in the last 12 months prior to starting study drug
  e. Other clinically significant heart disease (eg symptomatic congestive heart failure (LVEF <50%); uncontrolled arrhythmia; history of labile hypertension or poor compliance with an antihypertensive regimen.
  f. Uncontrolled Hypertension- if on one or more anti-hypertensive therapies.

In addition, the clinical study evaluations include regular ECG and echocardiographic monitoring at baseline and throughout the study.

Based on the experience of BRAF inhibitors, specific toxicities that may be encountered with RAF/MAPK pathway inhibition have been carefully considered. panRAF inhibitors have a broader breadth of activity compared to BRAF inhibitors, targeting (in addition to BRAF and CRAF) kinases such as KDR, p38, Src and GSK3B. It is therefore likely that they will result in a different side effect profile than existing BRAF inhibitors. A cautious approach will therefore be employed for the monitoring and management of such toxicities, with adjustment and adaptation of both monitoring schedules and investigations as new toxicities emerge.

2 TRIAL DESIGN

2.1 Clinical trial design

This is a first-in-human, open-label, Phase 1 trial of CCT3833 in patients with advanced solid malignancy. The trial will be conducted in two parts; an initial dose escalation phase (Part A), followed by an expansion stage (Part B, with three cohorts), wherein patients will be treated at the recommended Phase 2 dose, to further define tolerability and evaluate safety in a larger population and to support the design of subsequent trials with CCT3833 (see Table 4).

Part A, the dose escalation stage, will aim to establish the maximum dose that can safely be delivered to man, and establish what toxicities may arise. Patients with all-solid tumours will be recruited to this stage of the study, with no mandatory oncogene mutation sequencing being performed. As there is no evidence that panRAF inhibitor

therapy in the absence of specific oncogene mutations has deleterious effects, exclusion/inclusion of patients on this basis is felt to be unnecessary in the dose escalation stage. This will however be mandated (alongside a diagnosis of melanoma) in Part B, the dose expansion stage, and will be used to define the three cohorts of melanoma patients.

The starting dose for the first cohort in Part A is 20 mg. The bioanalysis of the PK samples from at least the first two patients in each cohort will be made available prior to dose escalation procedures. The dose escalation decision will be made on the basis of PK, safety, and tolerability of the dose after 3 patients have completed one 28-day cycle. Patients will continue with treatment until disease progression or failure to tolerate treatment. These patients will follow the treatment schedule provided in section 8.1 and Table 14.

Part B, the dose expansion stage, will further investigate the safety, tolerability, and early efficacy signals in BRAF- or RAS-mutant melanoma patients. The dose for Part B will be the recommended Phase 2 dose, selected based on the MTD and other data derived from Part A, the dose escalation phase. There will be 3 patient cohorts, defined by mutation and treatment history. All cohorts will receive the same dose for up to 12 months, or until disease progression. These patients will follow the treatment schedule provided in section 8.2 and Table 15.

Approximately 69 patients will be enrolled in this study in total, with up to 42 in Part A and approximately 27 in Part B. The total number of patients enrolled will depend upon the number of screen failures, number of dose escalations necessary, and number of evaluable patients.

The trial is expected to be open to recruitment for approximately 30-36 months. Patients will receive treatment with CCT3833 until disease progression or failure to tolerate treatment. It is anticipated that patient follow-up for survival status will be performed for up to 12 months after the last dose in Part B.

Table 4 Trial schematic

	Number of patients and sites	***Patient numbers per cohort***		
Part A: Dose Escalation	• n = up to 42 • Sites: ○ DDU, RM Sutton ○ CTU, The Christie, Manchester	• n = 3-6		
Part B: Expansion	• n = 27 at RP2D • Sites: ○ RM Chelsea ○ CTU, The Christie, Manchester	• BRAF mutant, BRAF inhibitor treatment naïve • N=9	• BRAF mutant with progression on BRAF inhibitor	• RAS mutant • N=9

- N=9

RP2D = recommended Phase 2 dose

3 CLINICAL STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary endpoints

Table 5: Primary study objectives and endpoints

Objective	Endpoint
To propose a recommended dose for further expansion phase drug evaluation by:	
g. Establishing the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of CCT3833.	a. The maximum tolerated dose is the dose at which no more than one patient out of up to six patients at the same dose level experience a highly probably or probably drug-related DLT as defined in the protocol. This dose level will be selected as the RP2D.
b. Assessing the safety and tolerability profile of CCT3833.	c. Determining causality of each adverse event (AE) to CCT3833 and grade according to NCI CTCAE v4.03.

3.2 Secondary endpoints

Table 6: Secondary objectives and endpoints

Objective	Endpoint
To determine the pharmacokinetic profile of CCT3833 in humans.	Assessment of plasma levels of CCT3833 for 48 hours between Days -7 to -3 before Cycle 1, and on Cycle 2, Day 1.
To explore possible anti-tumour activity of CCT3833 in patients with advanced solid tumours.	Any measurable response (clinical or radiological) in any of the patients, as determined by the RECIST criteria v1.1.
Determining the correlation between PK exposures and tolerability and/or efficacy (i.e. defining the safe therapeutic range).	Correlation of plasma levels of CCT3833 with markers of efficacy and adverse event reports.

3.3 Exploratory endpoints

Table 7: Exploratory objectives and endpoints

Objective	Endpoint
To investigate the pharmacodynamic profile of CCT3833 in humans and to establish a biologically-active dose range.	Correlation of plasma levels of CCT3833 against tumour shrinkage data from imaging.
Determining magnitude and duration of effect in biomarkers (including but not limited to ERK, phosphorylated-ERK, Cyclin D1, Ki-67, ADAM28, Caveolin1, Phospho-SRC, Total SRC, CD34) in surrogate and tumour tissue following CCT3833 administration.	Evaluation of a range of biomarkers from optional biopsies and blood samples taken at baseline, on-treatment, and at disease progression.
Identifying potential novel biomarkers/genetic alterations that can be utilized to track tumour burden, response to treatment, and potential mechanisms of resistance by genetic analysis of patient's optional blood and biopsy samples	Next generation sequencing of DNA/RNA extracted from optional biopsy and blood samples
Obtaining plasma samples for potential metabolite characterisation.	Any such investigation will be reported separately.

4 PATIENT SELECTION

4.1 Trial participants

The trial will initially recruit (in Part A) a patient population with advanced solid malignant disease, who may be treatment naïve or refractory to standard therapies, or for whom no standard therapies exist. Part B, the expansion stage will recruit only melanoma patients with either RAS or BRAF mutations.

4.2 Inclusion criteria

4.2.1 Inclusion criteria: dose escalation stage

Patients must meet ALL of the following criteria:

1. 18 years or over.
2. Written (signed and dated) informed consent and willing and capable of co-operating with study procedures, treatment and follow-up.
3. Histologically proven advanced or metastatic solid tumours.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
5. Life expectancy of at least 12 weeks.
6. Haematological and biochemical indices (within 7 days before the first dose of CCT3833) within the ranges shown below:
   a. Haemoglobin (Hb) ≥ 9.0 g/dL.

b. Absolute neutrophil count ≥ 1.5 x 10^9/L.
c. Platelet count ≥ 100 x 10^9/L.
d. Total bilirubin ≤ 1.5 x upper limit of normal (ULN), and Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x (ULN) (or ≤ 5 x ULN if elevated due to tumour).
e. Calculated creatinine clearance > 50 mL/min (based on Cockcroft-Gault calculation).

7. Negative pregnancy test for females of child-bearing age.

4.2.2 Inclusion criteria: dose expansion cohort

Patients must meet ALL of the above criteria and additionally meet the following criteria:

1. Histologically proven locally advanced (unresectable) or metastatic melanoma.
2. Documented presence of either BRAF or RAS mutations, as established by validated mutation testing from tumour biopsy.
3. Evidence of measurable disease (according to RECIST v1.1, Appendix 5).

4.3 Exclusion criteria:

Patients who meet ANY of the following criteria will not be eligible to participate.

Patients who have had any of the following within the last 4 weeks:

1. Radiotherapy (except for palliative reasons), endocrine therapy (except luteinizing hormone releasing hormone (LHRH) agonists for prostate cancer), immunotherapy or chemotherapy (6 weeks for nitrosoureas, Mitomycin-C and 4 weeks for other investigational medicinal products (IMP)) before treatment. (For patients recruited to Part B (dose expansion) from Part A (dose escalation), prior treatment with CCT3833 during Part A (dose escalation) is permissible.)
2. Major surgery within the last four weeks.
3. Has been a participant in another interventional research study (involving an IMP) within the last 4 weeks, or plans to participate in one whilst taking part in this study. Participation in an observational study would be acceptable.

Patients who have any of the following:

4. High medical risk because of non-malignant systemic disease including active, uncontrolled infection.
5. Known allergy to any pharmaceutical excipients.
6. Known to be serologically positive for Hepatitis B, Hepatitis C or Human Immunodeficiency Virus (HIV). Testing for these viruses is not mandatory.
7. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:

a. History or presence of ventricular tachyarrhythmia.
b. Presence of unstable atrial fibrillation (ventricular response > 100 bpm); patients with stable atrial fibrillation are eligible, provided they do not meet any of the other cardiac exclusion criteria.
c. Repeated presence of a prolonged QTc interval > 450 ms at baseline (as calculated by Fridericia method).
d. Unstable angina pectoris or acute myocardial infarction in the last 12 months prior to starting study drug.
e. Other clinically significant heart disease (e.g., symptomatic congestive heart failure (LVEF < 50%); uncontrolled arrhythmia; history of labile hypertension or poor compliance with an antihypertensive regimen).

8. Uncontrolled hypertension that remains uncontrolled on > 1 antihypertensive agent.
9. Symptomatic brain metastases (if present they must have been stable for > 3 months). Such patients must not be requiring systemic corticosteroid or enzyme-inducing anticonvulsant therapy.
10. Inability to take oral medication; impairment of GI function or GI disease that could interfere with drug absorption.
11. Have taken potent inducers/inhibitors of CYP3A4 and CYP2C8 liver enzymes within 2 weeks of the first administration of study drug, or have conditions that require the concomitant usage of such drugs during the course of the study.
12. Are taking warfarin as an oral anticoagulant; patients anticoagulated with low molecular weight heparin are not excluded from the trial.
13. Female patients who are pregnant or lactating, or have the ability to become pregnant. However, those female patients who have a negative serum or urine pregnancy test before enrolment and are using highly-effective contraception during the study and for 6 months afterwards, are considered eligible. Highly-effective contraception methods include:
    a. Total abstinence.
    b. Male or female sterilization.
    c. A combination of any two of the following:
        i. Oral, injected or implanted hormonal contraception.
        ii. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
        iii. Barrier methods of contraception: condom or diaphragm with spermicidal foam/gel/film/cream/vaginal suppository.
14. Male patients with partners of child-bearing potential, unless they agree to take measures not to father children by using one form of highly effective contraception as defined above, during the study and for 6 months afterwards. Men with pregnant

or lactating partners should be advised to use barrier method contraception to prevent exposure to the foetus or neonate.

15. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical study.

5 TRIAL PROCEDURES

5.1 Recruitment

Patients will be recruited to Part A of the study through the Phase 1 units at RMH, Sutton and Christie Hospital, Manchester. Recruitment to Part B will be coordinated by the melanoma units of each site. The assignment of a patient to a particular cohort will be coordinated by RM-CTU.

5.2 Informed consent

The patient must personally sign and date the latest approved version of the informed consent form before any trial specific procedures are performed, and between Day -28 and the first dose of CCT3833. Informed consent will allow registration into the screening stage of the trial, during which evaluations will determine eligibility. Following confirmation of eligibility, patients will proceed to trial entry.

Written versions of the participant information and informed consent will be discussed with the participants.

It will be clearly stated that the participant is free to withdraw from the trial at any time, for any reason, without prejudice to future care and with no obligation to give the reason for withdrawal. The patient will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the trial. As a minimum, the patient may consent after considering the information for no less than 1 day.

Written informed consent will be obtained by means of patient dated signature, and dated signature of the person who presented and obtained informed consent; the dates should be the same. The person obtaining consent must be suitably qualified and experienced, and have been delegated the responsibility to do so by the Chief Investigator/Principal Investigator (as evidenced by signing the trial delegation log). A copy of the signed informed consent will be given to the patient. The original signed form and information sheet must be retained in the Investigator trial file at the trial site.

5.3 Screening and eligibility assessment

At enrolment, each potential patient will provide informed consent prior to starting any study specific procedures. Each potential patient is assigned a unique patient identifier. If a patient withdraws from the study, then the identifier cannot be reused.

Demographic data and other characteristics will be recorded and will include: date of birth, gender, race and ethnicity according to local regulations. A standard medical, and

medication and surgical history will be obtained, along with review of the selection criteria with the patient.

Each patient will undergo Screening during the 28 days prior to admission, to confirm eligibility. Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study, provided the assessments fall within the protocol-specified period prior to the first dose of study treatment.

5.4 Randomisation and blinding

No randomisation will be performed for this trial. This is an open-label trial, therefore no blinding is necessary.

5.5 Patient evaluability

All patients who meet the eligibility criteria and receive at least one administration of CCT3833 will be evaluable for safety.

Patients who receive less than 75% of the planned doses of CCT3833 during the first treatment cycle (for reasons other than toxicity) will not be evaluable for dose review decisions. Patients who are not evaluable may be replaced.

All patients who meet the eligibility criteria, receive at least 75% of the planned doses of CCT3833 in the first treatment cycle, and have a baseline assessment of disease will be evaluable for disease response according the RECIST criteria v1.1 (Appendix 5). To be assigned a status of complete response (CR) or partial response (PR), changes in tumour measurement must be confirmed by repeat measurements performed no less than 4 weeks after the response criteria are met. To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once, and at least 6 weeks after the first dose of CCT3833 has been taken.

6 TREATMENT

6.1 Definition of treatment cycle

The first dose of continuous dosing defines Cycle 1 Day 1. All treatment cycles have a duration of 28 days. There will be no delays between cycles, i.e. Day 29 represents Cycle 2, Day 1.

6.2 Selection of the Phase 1 starting dose

The starting dose of CCT3833 is 20 mg, taken as two 10 mg capsules. The starting schedule is a once daily continuous dosing schedule, but other dosing regimens may be considered depending on tolerability and exposures

6.3 Treatment schedule

CCT3833 has been formulated into 5 mg, 10 mg 25 mg or 75mg hydroxy-propyl-methyl-cellulose (HPMC) capsules. A combination of these capsules will be combined to provide the appropriate daily dose.

A single dose will be given between Days -7 and -3 prior to commencing continuous dosing; this will be for clinical safety and pharmacokinetic assessment purposes.

The pharmacokinetics of the first dose in the first subject will be analysed with a rapid turnaround time before further patients are dosed. For the first dose administration at all dose escalation levels, patients will be admitted to (or required to stay close to) the clinical research facility for a period of 48 hours, for blood PK and ECG assessments, and to allow close observation of potential side effects. Vital signs including temperature, pulse rate and BP will also be assessed. The results of the bioanalysis of the pharmacokinetic sampling will not be required before commencement of the first continuously dosed escalation cohort the following week.

CCT3833 will then be taken continuously according to a daily schedule. The treatment schedule will be reviewed as the trial progresses and the dosing schedule may be amended during the course of the trial. If evidence of dose-limiting toxicities (DLTs) occur in early cohorts of dose escalation (or other emerging pharmacokinetic and/or pharmacodynamic data suggest it to be appropriate), the dosing schedule may be altered from once-daily dosing. For example, the single daily dose may be split into two (or more) daily doses to investigate whether a higher total daily dose could be delivered whilst avoiding DLTs. Similarly, a decision to explore intermittent dosing (for example, 2 weeks of continuous treatment followed by a 1 week break) may be made if the real-time monitoring of patients indicates this to be appropriate.

6.4 Definition of dose-limiting toxicity

The dose-limiting toxicity (DLT) is defined using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (Appendix 4). DLTs identified in Cycle 1 of treatment will inform the decision to dose escalate through the increasing dose levels. Significant toxicities and DLTs in later cycles will be considered throughout the treatment period and in determining the recommended Phase 2 dose.

A DLT is defined as a probably or highly probably drug related toxicity as detailed in Table 8.

Table 8: Dose-limiting toxicity definitions and criteria

Toxicity	Criteria
Any toxicity causing a decrease in treatment dose intensity	Inability to deliver > 75% of the planned dose intensity in a cycle due to CCT3833-related toxicity
Haematology	• Grade 4 neutropenia for > 1 week • Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding • Febrile neutropenia • Grade 4 anaemia (unless a specific cause of blood loss is identified)
Cardiovascular	• Any grade 3 or above • Hypertension (grade 3 or above) lasting more than 2 weeks despite optimal treatment
Skin	Any grade 3 or above, persisting for > 7 days despite optimal treatment
Metabolic	Grade 3 or above hyperglycaemia (measured in the fasted state)
Any other drug related G3/4 toxicity except:	• Alopecia • Nausea that is sub optimally managed • Vomiting that is sub optimally managed • Diarrhoea that is sub optimally managed • Constipation that is sub optimally managed
Any other toxicity that is considered dose-limiting in the view of the Investigator	

Baseline laboratory values are those reported before the first dose of CCT3833.

6.5 Definition of maximum tolerated dose

Part A of the trial aims to define the MTD of CCT3833.

A minimum of 6 evaluable patients is necessary to determine the MTD. A dose will be considered non-tolerated and dose escalation will cease if 2 or more patients experience a DLT at a dose level. Once the non-tolerated dose is defined, the MTD will be confirmed at the previous dose-level below the non-tolerated dose; a dose between the non-tolerated dose and the last tolerated dose may also be investigated. The recommended Phase 2 dose (RP2D) will be defined as either the MTD, or the highest dose that is tolerated and has demonstrated efficacy. The dose will be determined following discussion of all relevant study data.

6.6 Dose escalation scheme

Patients will be enrolled to ensure a minimum of 3 and a maximum of 6 evaluable patients per cohort. The dose level of CCT3833 will be assigned using all available data by the Sponsor in conjunction with the Safety Review Committee (SRC). Dose assignment will be made after considering the number of patients already enrolled at the current dose level, the number of DLTs (and any other drug related AEs) observed at the current dose level, and the number of patients enrolled who are at risk of developing a DLT.

The first patient in all cohorts will be treated for 7 days taken from Day 1, before the second and third patients can take their first dose of CCT3833 in parallel. Patients who receive less than 75 % of their planned doses in Cycle 1, taken from Day 1 onwards, for reasons other than toxicity will not be evaluable for assessment of DLT for dose review decisions and will be replaced in the cohort.

In order to make the decision to escalate the CCT3833 dose, three evaluable patients must have completed one cycle of treatment (28 days). The time between cohorts is therefore approximately 6 weeks.

The dose increases between cohorts will be up to 100%, i.e. doubling of the dose (dosed on a flat scale and not by body weight or body surface area), until a probable or highly probable drug-related CTCAE v4.03 (Appendix 4) Grade 3 AE (or grade 4 haematological toxicity) is reported. Subsequent dose increases between cohorts will be driven by reported safety data and available PK and PD data. The available PK data for all patients will be reviewed as part of the dose escalation data. PK data for a minimum of two patients in the current cohort will be required to inform dose review decisions. PK data for a minimum of two patients from the previous cohort will also be required.

6.7 Communication between trial sites

Effective communication of emerging safety data and precise coordination of patient recruitment and dose allocation is imperative for the safe and smooth conduct of this trial.

6.7.1 Trial management group

Part A will be conducted in two of the largest and most experienced Phase 1 clinical trial units in the UK that are not only well experienced in the running of first-in-human oncology studies, but also have significant collaborative history with each other on such trials. The units are therefore well used to the scientific rigour required in running such early phase trials, as well as the practicalities of effective cross-site communication. In this regard, regular (usually fortnightly) operational teleconferences will be convened between the PIs (and /or delegates) of both sites and the RM-CTU, to review patient recruitment and emerging toxicity (or other) data. This is the trial management group. If more frequent communication is required, further teleconferences (in addition to the routinely scheduled teleconferences) will be arranged.

6.7.2 Safety review committee

Specific dose escalation meetings will be conducted every 4-6 weeks, or when 3 patients have completed the 28-day DLT window, whichever is earlier. These will be to determine if the dose level has been tolerated by the patients and that it is safe to escalate the dose to the next level. Dose escalation decisions will be led by the SRC which will consist of:

- Chief Investigator or delegate
- Principal Investigator or delegate from each investigational site

- RM CTU operations manager or delegate
- Trial Statistician
- Senior Phase 1 trial clinician (who is not CI/PI)
- Senior melanoma trial clinician (who is not CI/PI)
- Chairperson (must be independent of the Investigators/institution)

Further internal or external experts may be included by the SRC as necessary.

Part B, the dose expansion stage, is being conducted in two large and experienced melanoma units who have also worked extensively together on trials on multiple previous occasions. The above described SRC will also convene at regular intervals (at least quarterly) to review the accumulating safety data from the trial during the dose expansion stage; more frequent meetings will be dictated by availability and severity of on-going safety information. They will meet (teleconference) within a week of any grade 4 toxicities or death, regardless of whether thought attributable to CCT3833 or not.

6.8 Dose escalation decisions

An SRC meeting will be triggered when three patients have had the opportunity to complete the first cycle of treatment. The safety data including a list of DLTs and all AEs will be reviewed, along with all other available data (including PK analyses from at least two subjects), in order to make the decision. When sufficient data are available to assess the existing cohort, the next dose level will be assigned according to the following:

- Proceed with dose escalation: If the data is available from three patients who have been treated in a cohort and no DLTs have been observed at that dose level, then dose escalation can be considered.
- Expand the cohort to further explore the dose level: If the data is available from three patients who have been treated in a cohort and one DLT has been observed at that dose level, then the cohort will be expanded to include six patients.
- De-escalate the dose: If two DLTs have been observed at any dose level, the dose will be de-escalated to either the previous dose level (expanding to include up to six patients) or an intermediate dose level will be explored. If the previous dose level already included a cohort of six patients then this will be identified as the MTD.
- Explore different dosing schedules or formulations: If the daily continuous dosing treatment schedule is not tolerated, then the frequency of dosing for subsequent patients may be reduced. Dose escalation will continue at the reduced schedule.
- Stop the dose escalation phase of the study.

The decisions of the SRC on the next dose level and/or dosing schedules will be documented and provided to the Investigators prior to dosing any new patients.

The RP2D to be further evaluated in Part B (expansion phase) will be determined by the SRC based on the MTD and observed safety profile, PK and PD data. During the expansion phase, the SRC will continue to monitor safety and will agree any action needed to refine the dose or dosing schedule.

6.8.1 Intra-patient dose escalation

Patients without disease progression or significant toxicity will be eligible for intra-patient dose escalation, which may occur at the end of every second treatment cycle, after at least 56 days on treatment. Such escalation would occur in addition to the three newly recruited patients allocated to the new dose level cohort, as long as at least 28 days of safety data was available for that dose level and the dose level had not been closed due to toxicity.

The decision of intra-patient dose escalation for each patient will be fully discussed and decided by the SRC. Those patients who have a dose escalation can be counted by the SRC for the purpose of considering further escalations. Additional PK samples will be collected from patients that have dose escalation at C2 D1 of the escalated dose regimen.

6.9 Dose modifications

6.9.1 Dose reductions

The dose of CCT3833 will be reduced to the previous dose level for any patient who experiences a DLT (which can occur during any cycle of treatment). Once the dose has been reduced, it should not be re-escalated. If any patient requires more than two dose reductions, the patient should be withdrawn from the study by the Principal Investigator.

6.9.2 Dose delays

If at the time of the scheduled start of the next cycle, any drug-related toxicities are still present and have not resolved to Grade 1 or to meet the eligibility criteria treatment should be delayed for up to 2 weeks until these toxicities have resolved to Grade 1 or to meet the eligibility criteria. If there is no recovery after a 2-week delay, the patient should be withdrawn from the study. In addition, a treatment delay of more than 28 days for reasons other than drug-related AEs will result in the patient being removed from the study.

6.9.3 Dose expansion cohort

Once a MTD is defined in Part A, Part B, the melanoma-specific expansion phase will begin at the defined RP2D in order to define the safety, tolerability, pharmacokinetics and pharmacodynamics and provide preliminary efficacy information on CCT3833.

Patients with metastatic or locally advanced (unresectable) melanoma will be recruited into clinically and molecularly defined groups (approximately 9 in each), namely:

1. BRAF mutant, BRAF inhibitor ‘treatment naïve’.

2. BRAF mutant, with progression on licensed BRAF inhibitor.
3. RAS mutant.

The total number of patients in this stage of the study will therefore be 27. Recruitment to cohorts will take place simultaneously rather than sequentially. This stage of the study will again operate at two sites, namely the Royal Marsden Hospital, London, and The Christie Hospital, Manchester.

Melanoma patients treated at the RP2D in the dose escalation phase of the study may continue on study treatment if re-screening confirms their eligibility. They can therefore be included in the efficacy analysis in the expansion stage of the study, in addition to, the 9 patients in the relevant cohort.

Melanoma patients treated at a dose escalation dose other than the recommended Phase 2 dose, who remain on treatment at the time of commencement of Part B, may also be re-screened and, if eligible, resume treatment at the RP2D as part of the expansion stage. Again, these patients will be recruited in addition to, the 9 patients in the relevant cohort.

Any melanoma patient identified with PD on CCT3833, who has not previously received licensed BRAF inhibitor therapy (i.e. Cohort 1), will be immediately offered treatment with the most appropriate approved alternative targeted therapy. This 'rescue route' will ensure that a patient's treatment is not compromised through trial participation.

During the expansion phase, the SRC will continue to monitor safety and will agree any action needed to refine the dose or dosing schedule.

6.10 Oncogene mutation sequencing

Identification of mutation status will be performed locally, from archival paraffin-embedded tumour samples. If archival tissue is not available, or is inadequate for testing, a fresh biopsy must be taken.

Historical tissue and tumour biopsies taken during the study will be sequenced for other clinically relevant mutations, either during this study, or after the reporting of this study. Patients in both the escalation and expansion stages will be asked to consent to this, and to the future potential testing of historical and biopsy tumour tissue, at the time of recruitment to the study.

6.11 Duration of treatment

Patients in Part A (dose escalation stage) may continue to receive CCT3833 as long as they are continuing to show clinical benefit, as defined by clinical or radiological (RECIST v1.1, Appendix 5) criteria.

Patients in Part B (dose expansion stage) will receive a maximum of 12 cycles of treatment. If they are continuing to show clinical benefit at this stage, treatment may be continued on a compassionate basis.

6.12 Discontinuation/withdrawal of participants from trial treatment

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Pregnancy.
- Ineligibility (either arising during the trial or retrospectively, having been overlooked at Screening).
- Serious deviation of the study protocol (including persistent patient attendance failure and persistent non-compliance).
- An AE (or SAE), which requires discontinuation of the trial medication or results in inability to comply with trial procedures.
- Withdrawal of consent.
- Evidence of disease progression.
- Withdrawal by the Investigator.
- Sponsor's decision to terminate the study.

All results of the evaluations and observations to the point of withdrawal, together with a description of the reasons for withdrawal from the study, must be recorded in the medical records and in the eCRF. Patients who are removed from the study due to AEs (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the eCRF and on the SAE report form where necessary.

6.13 Replacement of patients

Patients that withdraw but are evaluable for dose escalation decisions will not be replaced. Any patient that is withdrawn and is not evaluable will be replaced to ensure the minimum number of evaluable patients at each dose level in Part A. Patients may be replaced by another patient treated at the same dose level during the dose escalation phase if they fulfil at least one of the following criteria:

- Withdrawal from treatment prior to the end of Cycle 1 for reasons other than drug-related toxicity.
- Administration of less than 75% of planned doses of CCT3833 during Cycle 1 for reasons other than drug-related toxicity.

During Part B (the expansion stage) no replacement will be needed.

6.14 Definition of 'End of Trial'

The entire study will be stopped when:

- The drug is considered too toxic to continue treatment before the required number of patients being recruited; or
- The stated number of patients to be recruited is reached; or
- The stated objectives of the study are achieved.

It is the responsibility of the Sponsor to inform the Medicines and Healthcare products Regulations Agency (MHRA) and the Main Research Ethics Committee (REC) **within 90 days of the 'end of the study'** that the study has closed. In cases of early termination of the study, for example, due to toxicity, or a temporary halt, the Sponsor will notify the MHRA and the Main REC **within 15 days** of the decision and a detailed, written explanation for the termination/halt will be given. The Sponsor will ensure that end of trial report is provided to the licensing authority and REC within 12 months after the end of trial notification has been submitted.

The 'end of study' is defined as the date when the last patient has completed the 'Off-study' visit or the final follow-up visit (whichever is the latter). The maximum study evaluation period for a patient is 12 cycles (approximately 12 months), after which the patient would have an 'Off-study' visit performed.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented. In terminating the study, the Investigators must ensure that adequate consideration is given to the protection of the patient's interest.

All patients are allowed to continue with CCT3833 treatment beyond 12 cycles if they are receiving therapeutic benefit and providing drug supplies continue to be available. This will be either on the basis of compassionate use supply, or entry into an open safety protocol.

7 PHARMACEUTICAL INFORMATION

7.1 Pharmaceutical data

7.1.1 Formulation of CCT3833

CCT3833 is a poorly soluble crystalline compound. It is multi-polymorphic and one form, designated Form D, has been purified and typically has a particle size of about 15-20 µm. Form D readily absorbs and desorbs water, but is not a hydrate and has been selected as the form to take forward into clinical development.

The clinical trial formulation is a 1:3:0.5 ratio of CCT3833:Kollidon VA64:10% Kolliphor, which is spray-dried to produce a white powder suitable for filling into HPMC capsules. The clinical trial supplies will be available in HPMC capsules containing 5 mg, 10 mg, 25 mg and 75mg CCT3833. Further doses of capsules may be manufactured during the trial if required and details of any further manufacturing and development will be found in the Investigational Medicinal Product Dossier (IMPD). The capsule shells are opaque and each capsule strength will be differentiated by size.

7.1.2 Supply of CCT3833

The capsules will be packaged in 180 mL opaque bottles, with a child-proof lid; desiccant material will be included in the bottles. The manufacture, packaging and labelling of the

trial supplies is performed by Junipar Pharma Services, who will also be releasing the finished product in accordance with EU regulations for use in the clinical trial. The clinical trial labels will be prepared in accordance with Annex 13 of the GMP regulations.

7.1.3 Storage conditions of CCT3833

The bottles will be labelled for storage between 15 and 25 ˚C.

7.1.4 Stability of CCT3833

Stability studies are on-going, with CCT3833 capsules packaged in representative clinical presentations in accordance with ICH stability protocols, including room temperature and accelerated storage conditions. In addition, stability studies are on-going with GMP batches of CCT3833 drug substance at room temperature and accelerated conditions.

At the time of the initiation of the clinical trial there is anticipated to be stability data from both real-time and accelerated conditions from 3 batches of GMP drug substance and two batches of finished product to support a 12 month shelf life. This will be subject to the samples meeting the shelf life specification. The stability studies will continue throughout the trial to support an extension of the shelf life of the supplies as necessary.

7.2 Dispensing of CCT3833

Sufficient capsules of CCT3833 must be dispensed on each occasion to cover the prescribed dose, over the period to the next scheduled dispensing. The CCT3833 must be dispensed into a suitable container with a child proof closure. Patients must be instructed to ensure that CCT3833 is kept out of sight and reach of children.

7.3 CCT3833 administration

CCT3833 is an oral therapy in capsule form that, with the exception of doses given during the admissions for PK sampling, will be self-administered by patients, on a daily basis, at home.

CCT3833 must be taken with food. On days when PK samples are collected, all patients will be advised of a standard meal composition (approximately 600-700 kcal) that must be taken alongside each dose of their medication (www.fda.gov/downloads/.../Guidances/UCM126833.pdf).

Patients should aim to take the drug at the same time each day. Should a patient miss a scheduled dose in error, for example, by forgetting to take the drugs, then CCT3833 may be administered up until 3 hours after the scheduled dose. Should a patient miss a scheduled dose due to vomiting, the patient should not re-take the dose and should wait until their next scheduled dose.

7.4 Compliance with trial treatment

CCT3833 must only be used as directed in this protocol. Details of treatment with CCT3833 for each patient will be recorded in the eCRF.

Patients will be given the appropriate number of capsules to take with them to cover a single cycle of treatment, with a small overage. Patients will be asked to complete a study diary to document drug administration and to bring any remaining capsules and empty containers with them to each study visit. The Investigator should make every effort to ensure patients' compliance to treatment.

7.5 CCT3833 accountability

Accurate records of all CCT3833 shipments, capsules dispensed and returned must be maintained. CCT3833 supplies are to be used only in accordance with this protocol and under the supervision of the Investigator. The study personnel at the investigational site will account for all drugs dispensed and returned and for appropriate destruction.

7.6 Concomitant medication and treatment

Concomitant medication may be given as medically indicated. Details of the medication, including doses, frequency, route and start and stop dates, must be recorded in the patient's medical records. See Appendix 3 for a list of concomitant medications to be avoided.

The patient must not receive other anti-cancer therapy or investigational drugs while on the study.

7.7 Post-trial treatment

At the end of the study, if patients remain on treatment and are deemed to be deriving on-going clinical benefit, efforts will be made to continue treatment, unless the drug is no longer available due to the cessation of drug manufacture. For any such patients continuing drug treatment as part of a 'compassionate use programme', separate documentation is being developed to support the on-going monitoring of these patients for the time they remain on therapy after the end of the trial.

8 INVESTIGATION SCHEDULE

8.1 Part A (dose escalation stage)

8.1.1 Pre-treatment evaluations

8.1.1.1 *Baseline evaluations*

The following must be performed/obtained between Day -28 and the first dose for PK:

- Written informed consent.
- Demographics.
- Medical History.
- Height.
- Recording of symptoms.
- Review of concurrent medications.
- Echocardiogram (within 28 days of Day 1).

- Radiological imaging with target lesion assessment by RECIST v1.1 (Appendix 5) (within 28 days of Day 1).
- Tumour biopsy – optional.

The following must be performed between Day -7 and the first dose for PK:

- Physical examination.
- Clinical disease assessment (if applicable).
- ECOG Performance status, weight and vital signs.
- Laboratory investigations: including full blood count, clotting, urea and electrolytes, creatinine, ALT, AST, albumin, total protein, total bilirubin, calcium, LDH, creatine kinase, ESR, CRP, glucose, troponin I, HbA1c, magnesium and phosphate, tumour markers (as appropriate).
- Urinalysis (bHCG).
- ECG.

Baseline imaging must document all areas of disease present (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded clearly. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography, including a ruler to estimate the size of the lesion, is strongly recommended.

All radiological assessments must be performed between Day -28 and before starting treatment. The interval between the last anti-cancer therapy and these measurements must be at least 28 days. All clinical measurements to assess response must be done within 7 days before the patient starting treatment. Tumour lesions that are situated in a previously irradiated area can be included as measurable disease if they are clearly progressing at the time of initiating systemic therapy.

8.1.2 On-treatment assessments

8.1.2.1 *Pharmacokinetic evaluations*

During the dose escalation phase of the study, patients will be admitted (or required to stay close) to the clinical research facility for the administration of the first single dose (at Day-7 to Day -3) and thereafter for 48 hours, to allow blood sampling for PK to be collected. A second admission will also be required for 24 hours from Cycle 2, Day 1 (± 3 days), to allow further PK sampling (including patients that have intrapatient dose escalation). Patients will be advised of a standard meal (600 – 700 kcal) to be consumed prior to dose administration.

The sampling schedule is currently as defined in Table 9 below, but may be adjusted later if the emerging PK data suggest alternative time points would be more informative. Data will be used to determine PK parameters including:

- C_{max}
- T_{max}
- AUC_{0-t}
- AUC_{inf}
- $T_{1/2}$

Table 9: PK sampling schedule

Days (D)	Sample times (in hours) relative to dose*	Period of sampling relative to dose
Single dose (D-7 to D-3)	0	Pre-dose
Single dose (D-7 to D-3)	0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48	Post-dose
Cycle 2, Day 1-2 (±3 days)[+]	0	Pre-dose
Cycle 2, Day 1-2 (±3 days) [+]	0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24	Post-dose

*±5 min for first hour, ±10 min for 1.5-3 hours, ±15 min for 4-8 hours, ±1 hour for 12 hours, ±2 hours for 24/48 hour samples.

[+]The same sampling schedule and timepoint will be used for patients that are dose escalated on C2D1 of the increased dose

At each timepoint, 4 mL of blood will be collected into 4 mL K_2EDTA tubes. Sample processing, storage and shipment details will be described in the Laboratory Manual.

Bioanalytical analysis of plasma levels of CCT3833 will be performed by Covance UK. Samples for fast-turnaround analysis (supporting dose escalation decisions) will be analysed and quality controlled data generated within 48 hours from receipt of samples. This data will be analysed by a PK specialist, taking a further 24 hours to generate preliminary PK parameters and interpretation for use in the dose escalation meetings. Definitive PK parameter generation, using actual elapsed blood sampling times, will be performed upon release of final bioanalytical data. Any unused samples will be retained at ICR or another laboratory for possible metabolic profiling assessments to be reported separately .

Additional evaluations to be performed during the PK admissions are as follows:

- AE evaluation.
- Concurrent medications.
- ECOG performance status (Appendix 2) and weight.
- Physical examination.
- Intensive monitoring of vital signs will take place during the single dose PK admission between Day -7 and Day -3. During this admission, measurement will be taken:
  - Before dosing.
  - Every 30 minutes for 4 hours post dosing.

- Single standard ECGs will be conducted timed to coincide with the expected T_{max} (e.g. 4 hours post-dose and 24 hours post-dose).

8.1.2.2 *Safety and tolerability assessments*

Clinical review

Patients will be clinically reviewed on a weekly basis (± 1day) starting from Cycle 1, Day 1. The reviews will be repeated on a weekly basis (± 1day) (i.e. Cycle 1 Days 8, 15, and 22; Cycle 2 Days 1, 8, 15, and 22) until 8 weeks follow-up have been completed. If no DLTs are encountered, the visit frequency will be reduced to fortnightly (± 1day), for a further 8 weeks (i.e. Cycle 3 Days 1 and 15; Cycle 4 Days 1 and 15). Again if no further DLTs are observed, the visit frequency will be reduced to every 4 weeks (± 1day) (i.e. Cycle 5 Day 1, Cycle 6 Day 1, etc.) until disease progression.

Physical examination

A complete physical examination (including skin review) should be performed on Day 1 (± 1day) of each study cycle, and at the end of treatment. Additional examinations may be performed at the Investigator's discretion, if clinically indicated.

Weight

This will be measured on Day 1 (± 1day), of each cycle and at the end of treatment.

Vital signs

Intensive monitoring of vital signs (temperature, pulse, blood pressure and oxygen saturation) will take place during the single dose PK admission between Day -7 and Day -3. During this admission, measurement will be taken:

- Before dosing
- Every 30 minutes for 4 hours post dosing

Thereafter vital signs will be measured as per the clinical review schedule outlined above, and at the Off-study visit.

Laboratory evaluations

Full haematological and biochemical analysis, as described for baseline, should be performed as per the clinical review schedule (± 1 day):

- Cycle 1-2 Days 1, 8, 15, and 21.
- Cycle 3-4 Days 1 and 15.
- Cycle 5 Day 1and Day 1only of all subsequent cycles (assuming no DLTs encountered in expansion phase).
- End of treatment (±3 days).

ECG

Single standard ECGs will be conducted during the single dose PK admission timed to coincide with the expected T_{max} (e.g. 4 hours post-dose and 24 hours post-dose).

Thereafter, ECGs will be performed as per the clinical review schedule outlined in Table 12, with specific review of the QTc interval using Frederica's correction.

Echocardiography

This will be performed after 1 month (±3 days) on treatment to evaluate for any evidence of LV dysfunction. Thereafter, no routine echocardiography is scheduled, but may be performed as clinically indicated.

8.1.2.3 *Efficacy assessment*

All patients who meet the eligibility criteria, receive at least two cycles of CCT3833 and have a baseline assessment of disease and assessment of disease at the end of Cycle 2 will be evaluable for response. Efficacy will be evaluated using CT scans of the chest/abdomen/pelvis performed after 8 weeks of being on a stable dose, or more frequently, when clinically indicated. If patients undergo intra-patient dose escalation, the interval between scans may exceed 8 weeks in order to ensure a period of 8 weeks on a stable dose has been established. Clinical disease assessment should be performed every 4 weeks.

All lesions measured at baseline must be measured at every subsequent disease assessment, and recorded clearly. All non-measurable lesions noted at baseline must subsequently be noted as present or absent.

All patients, who are removed from the study for reasons other than PrD, must be re-evaluated at the time of treatment discontinuation, unless a tumour assessment was performed within the previous 4 weeks.

All patients discontinuing the study for PrD should have their disease progression documented by radiological evaluation. If a tumour biopsy is to be completed, the biopsy should be completed prior to radiological assessment.

To be assigned a status of CR or PR, changes in tumour measurements must be confirmed by repeat measurements performed no less than 4 weeks after the response criteria are met. To be assigned a status of SD, follow-up measurements must have met the SD criteria at least once, and at least 6 weeks after the first dose of CCT3833 has been taken. Should rapid tumour progression occur before the completion of two cycles of CCT3833 treatment, the patient will be classified as having early progression (EP). Tumour response should be classified as "not evaluable" (NE), only when it is not possible to classify it under another response category, for example, when baseline and/or follow-up assessment is not performed or not performed appropriately.

8.1.2.4 *Biomarker assessment*

Biomarker studies will be performed under the supervision of Professor Richard Marais, at the CRUK Manchester Institute and Professor Caroline Springer at ICR, and are included as exploratory objectives of the trial. Anonymised information may be provided to companies and government agencies if the Institute of Cancer Research or a partner organisation ever seeks an approval to licence CCT3833 as an anti-cancer treatment in either Europe or any other part of the world. The samples may be analyzed in laboratories in the US, Switzerland and the EU and may be shared with other researchers but the samples will not be shipped or distributed to any other non-EU countries.

In Part A (the dose escalation phase), patients in all cohorts will be asked (optional) to provide fresh core-needle tumour samples at the following time points:

- Pre-treatment: specified as between Day -28 and the first PK admission (Day -7 to Day -3).
- On treatment: Cycle 2 Day 1 (± 3 days).
- At disease progression.
- For patients enrolled at the Christie Hospital for the pre-treatment time point, tumour samples will be split in three; a third of the biopsy will be snap frozen in liquid nitrogen and stored at -80°C, a third of the biopsy will be fixed in formalin and a third of the biopsy will be taken to the Molecular Oncology lab for assessment and implanting subcutaneously in immunodeficient mice for the establishment and development of patient-derived xenografts.
- For patients enrolled, at Royal Marsden the pre-treatment time point, tumour samples will be split in three; a third of the biopsy will be snap frozen in liquid nitrogen and stored at -80°C, a third of the biopsy will be fixed in formalin and a third of the biopsy will be taken to the GOT team lab for assessment and implanting subcutaneously in immunodeficient mice for the establishment and development of patient-derived xenografts.

For all other time points for patients enrolled at The Christie Hospital and the Royal Marsden Hospital, tumour samples will be split in two; half of the biopsy will be snap frozen in liquid nitrogen and stored at -80°C, and the other half will be fixed in formalin.

The specific timing of these biopsy collections may be adjusted later if the emerging PK and PD data suggest an alternative time point would be more informative.

For the formalin-fixed samples:

Samples will be analysed for biomarkers by IHC, including but not limited to:

- ERK
- Phosphorylated ERK
- Cyclin D1

- Ki67
- ADAM28
- Caveolin1
- Phospho-SRC
- Total SRC
- CD34

For the snap frozen samples:

DNA and RNA will be extracted from the frozen samples for genetic analysis. DNA and RNA will be analysed by next generation sequencing methodologies. The samples can also be used to study the presence, activity or changes in levels of pharmacodynamic biomarkers such as but not limited to p-ERK and p-SRC.

For the sample for mouse implantation:

The sample will be kept in a tube without medium or PBS at room temperature and will be implanted subcutaneously in the flank of immunodeficient mice to establish and develop patient derived xenografts(PDXs). These tumours will be analysed genetically by next generation sequencing methodologies. Biomarkers as described above will be evaluated by IHC and tumour sensitivity will be evaluated in vivo.

Optional research blood samples will be collected from consenting patients at the following timepoints:

Set 1 for biomarker studies to be collected in conjunction with pharmacokinetic evaluation (PK) blood samples (including patients that have intrapatient dose escalation; see section 8.1.2.1 and Table 9): – both sites:

- Single dose (Day -7 to Day-3): pre-dose (baseline), 4, 8, 24 and 48 hours post dose – 5ml per time point, collected into EDTA tubes
- Cycle 2, Day 1 – pre-dose (baseline), 4, 8, and 24 hours post dose – 5ml per time point, collected into EDTA tubes

Peripheral blood mononuclear cells (PBMCs) will be extracted from these samples and used as a surrogate to tumour tissue to test for pharmacodynamic effects of the drug. The specific timing of these blood samples may be adjusted later if the emerging PK and PD data suggest an alternative time point would be more informative.

Set 2 for genetic analysis and CTC collection – both sites:

- Baseline

- On treatment: Cycle 2, day 1(± 3 days).
- On treatment: thereafter at the start of every second cycle (i.e. Cycle 4, day 1 (±3 days), Cycle 6, day 1 (±3 days) etc)
- At disease progression.

The specific timing of these blood samples may be adjusted later if the emerging PK and PD data suggest an alternative time point would be more informative.

In most cases, these samples will be collected in 2 Cell Save tubes (10ml tube) and analysed for cfDNA and circulating tumour cells (CTCs). CTCs will be enumerated and characterized with experimental platforms. cfDNA will be isolated from the plasma for genetic analysis by next generation sequencing methodologies. Germline DNA will be extracted from the whole blood or peripheral blood mononuclear cells (PBMC) for genetic analysis. DNA and RNA samples will be analysed by next generation sequencing methodologies.

At the pre-treatment time point, a third blood tube (10ml) will be collected in EDTA and will be processed in the local laboratory (ICR or Molecular Oncology lab at CRUK Manchester Institute). CTCs will be isolated with experimental systems and will be implanted subcutaneously in immunodeficient mice to establish CTC-derived Xenografts (CDXs). These tumours will be analysed genetically by next generation sequencing methodologies. Biomarkers as described above will be evaluated by IHC and tumour sensitivity to drugs will be evaluated *in vivo*.

For all the other time points, only 2 Cell Save tubes (2x10ml) will be collected and analysed for CTCs and cfDNA studies as described above.

Samples collected at Christie will be retained in storage at CRUK Manchester Institute and samples collected at Royal Marsden will be retained in storage at ICR for use in future research. All samples will be collected, processed and stored according to the laboratory manual.

A summary of exploratory samples and time points is shown in Table 10 below:

Table 10: Details of research samples and schedule: Part A

Sample	**Pre-treatment (Day-28 to first PK admission (Day -7 to Day-3)**	**Day-7 to Day -3 admission (single dose)**	**C2D1(±3 days)**	**C4D1(±3 days)**	**C6D1(±3 days)**	**Every 2 cycles thereafter (ie C8D1 etc)**	**At Disease Progression**
Tumour Biopsy	X[1]		X[2]				X[2]
Biomarker blood sample (up to 5x5ml EDTA		X 0, 4,8, 24,48h	X 0,4, 8, 24h				

CTC Sample (1x10ml cell save)	X		X	X	X	X	X
ctDNA/genomic sample (1x10ml CellSave)	X		X	X	X	X	X
CDX Sample (1x 10ml (EDTA)	X						

[1] Tumour sample will be split in three; a third of the biopsy will be snap frozen in liquid nitrogen and stored at -80°C, a third of the biopsy will be fixed in formalin and a third of the biopsy will be taken to the Molecular Oncology lab for further processing and implanting subcutaneously in immunodeficient mice for the establishment and the development of patient-derived xenografts. If only a small sample is obtained that cannot be split, the entire sample will be snap frozen

[2] Half of the biopsy will be snap frozen in liquid nitrogen and stored at -80°C, and the other half will be fixed in formalin. If only a small sample is obtained that cannot be split, the entire sample will be snap frozen

8.1.3 Off-study evaluations

These must be performed 28 days (± 3days) after the last dose of CCT3833, and should include the following as a minimum:

- Assessment of AEs and concurrent medications.
- ECOG Performance status.
- Physical examination and weight.
- Vital signs.
- Blood tests (including for tumour markers, if applicable).
- ECG.
- Radiological/clinical disease assessment.

8.1.4 Subsequent follow-up

During Part A (the dose escalation phase), if any AEs and SAEs are considered to have a possible – highly probable relationship to CCT3833, and are still present at the Off-study visit, then the patient will be followed up on a monthly basis until resolution to baseline or stabilisation of the events, unless another anti-tumour treatment is started.

For those Part A patients without any ongoing AEs, no further follow-up will be performed after the Off-study visit.

8.2 Part B (dose expansion stage)

8.2.1 Pre-treatment evaluations

8.2.1.1 *Baseline evaluations*

The following must be performed/obtained between Day -28 and Cycle 1 Day 1:

- Written informed consent.

- Demographics.
- Medical history.
- Availability of historical tumour biopsy (for confirmation of mutation status).
- Height and ECOG performance status.
- Recording of symptoms.
- Review of concurrent medications.
- Echocardiogram (within 28 days of Day 1).
- Radiological imaging (within 28 days of Day 1).
- Tumour biopsy – optional.

The following must be performed between Day -7 and Cycle 1 Day 1:

- Physical examination.
- Clinical disease assessment (if applicable).
- Performance status, weight and vital signs.
- Laboratory investigations: including full blood count, APTT, PT, urea, sodium, potassium, creatinine, ALT, AST, albumin, total protein, total bilirubin, alkaline phosphatase, calcium, LDH, creatine kinase, ESR, CRP, glucose, HbA1c, troponin I, magnesium and phosphate, tumour markers (as appropriate).
- Urinalysis (bHCG).
- ECG.

Baseline imaging must document all areas of disease present (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded clearly. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography, including a ruler to estimate the size of the lesion, is strongly recommended.

All radiological assessments must be performed between Day -28 and before starting treatment. The interval between the last anti-cancer therapy and these measurements must be at least 28 days. All clinical measurements to assess response must be done within 7 days before the patient starting treatment. Tumour lesions that are situated in a previously irradiated area can be included as measurable disease if they are clearly progressing at the time of initiating systemic therapy.

8.2.2 On-treatment assessments

8.2.2.1 *Safety and tolerability assessments*

Clinical review

Patients will be clinically reviewed on Cycle 1 Day 1 (± 1day). The review will be repeated on Cycle 1 Day 15 (± 1day) and then again on Cycle 2 Day 1 (± 1day). If no DLTs

are encountered, the visit frequency will be monthly (± 1day) thereafter (i.e. Cycle 3 Day 1, Cycle 4 Day 1) until disease progression.

Physical examination

A complete physical examination (including skin review) should be performed on Day 1 (± 1day) of each study cycle, and at the end of treatment. Additional examinations may be performed at the Investigator's discretion if clinically indicated.

Weight

This will be measured on Day 1 (± 1day) of each cycle and at the end of treatment

Vital signs

Vital signs will be measured as per the clinical review schedule outlined above, and at the Off-study visit.

Laboratory evaluations

Full haematological and biochemical analysis (as described at baseline) should be performed as per the clinical review schedule:

- Cycle 1 Day 1 (± 1day), and Day 15(± 1day).
- Cycle 2 Day 1(± 1day) and Day 1(± 1day) of all subsequent cycles (assuming no DLTs encountered in expansion phase).
- End of treatment.

ECG

Single standard ECGs will be performed as per the clinical review schedule, with specific review of the QTc interval using Frederica's correction.

Echocardiography

This will be performed after 1 month (±3 days) on treatment to evaluate for any evidence of LV dysfunction. Thereafter, no routine echocardiography is scheduled, but may be performed as clinically indicated.

8.2.2.2 *Efficacy assessment*

All patients who meet the eligibility criteria, receive at least two cycles of CCT3833, and have a baseline assessment of disease at the end of Cycle 2, will be evaluable for response. Efficacy will be evaluated using CT scans of the chest/abdomen/pelvis, performed every 8 weeks, or more frequently when clinically indicated. Clinical disease assessments should be performed every 4 weeks.

All lesions measured at baseline must be measured at every subsequent disease assessment, and recorded clearly. All non-measurable lesions noted at baseline must be subsequently noted as present or absent. At baseline, a brain CT or MRI must be

performed to assess for brain disease. If treated/stable brain metastases are documented at baseline, brain imaging should be continued throughout the study.

All patients who are removed from the study for reasons other than PrD, must be re-evaluated at the time of treatment discontinuation, unless a tumour assessment was performed within the previous 4 weeks.

All patients discontinuing the study for PrD should have their disease progression documented by radiological evaluation. If a tumour biopsy is to be completed, the biopsy should be completed prior to radiological assessment.

To be assigned a status of CR or PR, changes in tumour measurements must be confirmed by repeat measurements performed no less than 4 weeks after the response criteria are met. To be assigned a status of SD, follow-up measurements must have met the SD criteria at least once, and at least 6 weeks after the first dose of CCT3833 has been taken. Should rapid tumour progression occur before the completion of two cycles of CCT3833 treatment the patient will be classified as having early progression (EP). Tumour response should be classified as “not evaluable” (NE), only when it is not possible to classify it under another response category, for example, when baseline and/or follow-up assessment is not performed or not performed appropriately.

8.2.2.3 *Biomarker assessment*

The samples and schedule for biomarker assessment will be the same in Part B as in Part A, with the exception that there will be no PBMC biomarker blood sampling. See section 8.1.2.4 for full details. A summary of the samples and time points is shown in the Table 11 below. The specific timing of these biopsies and blood samples may be adjusted later if the emerging PK and PD data suggest an alternative time point would be more informative.

Table 11: Details of research samples and schedule: Part B

Site	Sample	Pre-treatment	C2D1 (± 3 days)	C4D1 (± 3 days)	C6D1 (± 3 days)	Every 2 cycles thereafter (i.e. C8D1 etc)	At disease progression
Christie	Tumour Biopsy	x [1]	x [2]	-	-	-	x [2]
	CTC Sample (1x 10ml CellSave)	x	x	x	x	x	x
	cfDNA/ Genomic Sample (1x 10ml CellSave)	x	x	x	x	x	x
	CDX Sample (1x 10ml EDTA)	x	-	-	-	-	-
Royal Marsden	Tumour Biopsy	x [2]	x [2]	-	-	-	x [2]
	Blood Sample (2x 10ml CellSave)	x	x	x	x	x	x

[1] Tumour sample will be split in three; a third of the biopsy will be snap frozen in liquid nitrogen and stored at -80°C, a third of the biopsy will be fixed in formalin and a third of the biopsy will be taken to the Molecular Oncology lab for further processing and implanting subcutaneously in immunodeficient mice for the establishment and the development of patient-derived xenografts. If only a small sample is obtained that cannot be split, the entire sample will be snap frozen

[2] Half of the biopsy will be snap frozen in liquid nitrogen and stored at -80°C, and the other half will be fixed in formalin. If only a small sample is obtained that cannot be split, the entire sample will be snap frozen

8.2.3 Off-study evaluations

These must be performed 28 days (± 3days) after the last dose of CCT3833, and should include the following at a minimum:

- Assessment of AEs and concurrent medications.
- ECOG Performance status.

- Physical examination and weight.
- Vital signs.
- Blood tests (including for tumour markers).
- ECG.
- Radiological/Clinical disease assessment.
- Subsequent tumour biopsy – optional.

8.2.4 Subsequent follow-up

In Part B (the expansion stage), a case report form entry should be completed at each hospital visit until objective disease progression has been recorded, or a maximum total of 12 cycles of treatment have been delivered, whichever occurs first. Responding patients may continue to receive treatment on a compassionate basis beyond 12 cycles.

Any patients who have ongoing treatment-related toxicities will be followed up on a monthly basis until resolution to baseline or stabilisation of symptoms, unless another anti-tumour treatment is started.

Once treatment has been completed, patients will be followed up for 12 months, for survival status only. This will conducted via telephone interviews.

Table 12: Study flow chart- Dose escalation phase

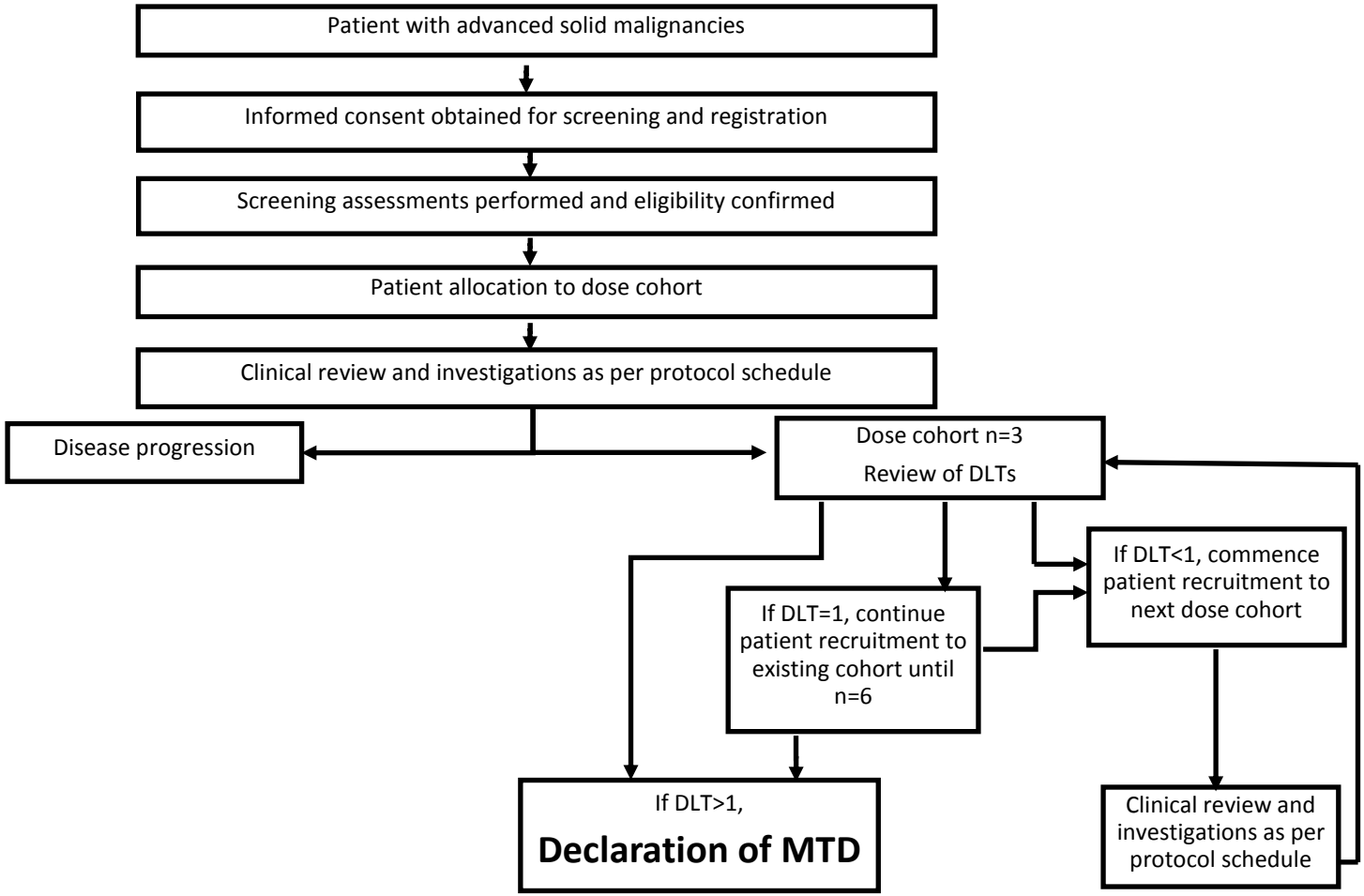


Table 13: Study flow chart- Dose expansion phase

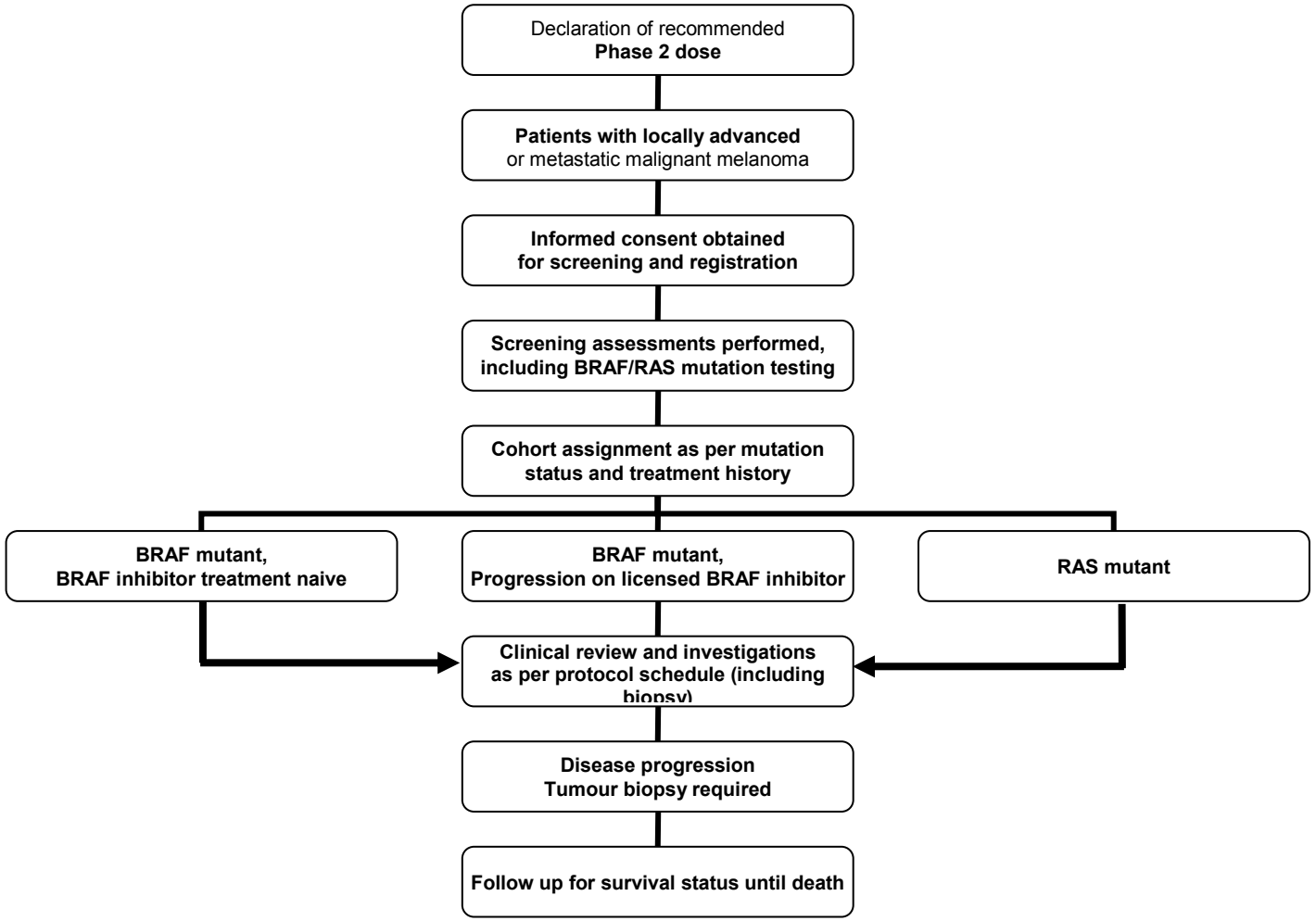


Table 14: Schedule of events- Dose escalation stage

Observation/Investigation	Pre-study		First dose for PK	Standard evaluations for each cycle of CCT3833; 1 cycle = 28 days						Off study	Follow up (for AE until resolution)
	Between Day -28 and first PK dose	Between Day -7 and first PK dose	D-7 to D-3	Cycle 1, Day 1 (± 1day)	Day 8 (±1day)	Day 15 (±1day)	Weekly thereafter until C3D1 (± 1day)	Fortnightly thereafter until C5D1 if no DLT observed (± 1day)	Monthly thereafter if no DLT observed (± 1day)	(± 3 days)	Monthly
Written informed consent	x										
Demographics and height	x										
Medical history	x										
Availability of historical tumour biopsy	x										
Radiological assessment[a]	x			At end of every 2 cycles on a stable dose							
Clinical disease assessment (if applicable)		x		At end of every cycle						x	
AE evaluation	x		x	x	x	x	x	x	x	x	x[k]
Concurrent medications	x		x	x	x	x	x	x	x	x	
Urinalysis (bHCG)[b]		x									
Tumour serum markers (if applicable)		x		At end of every cycle						x (unless performed within previous 6 weeks)	
Optional tumour biopsy[c]	x						x (C2D1 only)			x	
Optional CTC/genetics research blood sample[d]	x			x (C2D1) and thereafter every 2 cycles (i.e. C4D1, C6D1 etc)						x	
Optional PBMC research blood sample[e]			x				x (C2D1 only)				
ECOG performance status (Appendix 2)	x	x	x	x	x	x	x	x	x	x	
Physical examination[f]		x	x	x					x	x	
Weight		x	x	x					x	x	
Vital signs[g]: temperature, pulse, BP, oxygen saturation		x	x	x	x	x	x	x	x	x	
Laboratory tests[h]		x		x	x	x	x	x	x	x	x[k]
ECG		x	x	x	x	x	x	x	x	x	
Echocardiogram[i] (±3 days)	x						x (C2D1)				

Blood for PK assays[j]			x				x (C2D1)				

a) Radiological assessment using CT or MRI as appropriate.
b) If the patient is a woman of child bearing potential.
c) Tumour tissue needle biopsies (10mg material required) for pharmacodynamics assessment will be optional for patients in Part A (dose escalation stage). The sampling timepoints will be pre-dose between Day -28 and the first dose for PK between Day-7 and -3 and at C2D1 (±3 days), and when the patient is withdrawn from treatment.
d) Research blood samples for circulating tumour cell collection (2-3 x 10mL) will be requested (optional) from patients in Part A (dose escalation stage). The sampling points will be pre-dose between Day -28 and the first dose for PK (between Day-7 and Day -3), at Cycle 2 Day 1 (±3 days) and thereafter every 2 cycles (i.e. Cycle 4 Day 1, Cycle 6 Day 1 etc), and when the patient is withdrawn from treatment.
e) Research blood samples for PBMC collection (4-5 x 5ml) will be requested (optional) from patients in Part A (dose escalation stage). The sampling time points will be alongside the PK blood samples: namely pre-dose and following single dose administration (on Day -7 to Day -3) at 4, 8, 24 and 48 hours post-dose, and alongside the PK blood samples on Cycle 2, Day 1 (±3 days) at 0, 4, 8, 24 hours post-dose.
f) Complete physical examination to be performed pre-study, then all examinations can be symptom-directed performed on Day 1 of each cycle
g) Temperature, pulse rate, blood pressure and oxygen saturation rate should be performed pre-dose and then repeated every 30 mins (±5 min) for the first 4 hours post-dose at the first dose for PK (between Day-7 to-3). Vital signs should be repeated each week of Cycles 1 and 2, and then on D1 and D15 from Cycle 3 onwards at the discretion of the Investigator, and reduced again to once a month from Cycle 5 onwards.
h) Laboratory tests will be performed alongside each clinical visit; clinical laboratory assessments should therefore be performed on Days 1, 8, 15, 22 during Cycles 1 and 2. The frequency can be reduced to Days 1 and 15 from Cycle 3 onwards at the discretion of the Investigator, and reduced again to once a month (pre-dose on Day 1) from Cycle 5 onwards. In the event of a grade 4 neutropenia or grade 4 thrombocytopenia, a full blood count must be performed at least on Day 5 after the onset of the event to determine if a DLT has occurred. Continue close monitoring until resolution to grade 3 or less. Non fasting glucose, and LDH are required for biochemistry. If non fasting glucose >7.8 mmol/l, repeat as a fasting glucose. If this too demonstrates grade 3 hyperglycaemia, a formal glucose tolerance test should be undertaken, and appropriate management of hyperglycaemia initiated.
i) An echocardiogram will be performed pre-study and at the start of Cycle 2 (±3 days). It will then only be repeated as clinically indicated.
j) 4 mL blood samples for PK assessment will be taken for all patients between Day-3 and Day-7, and on C2D1 at twelve time points: pre-dose on the day of dosing, 15 min (± 5 min), 30 min (± 5 min), , 1 h (± 5 min), 1.5 h (± 10 min), 2 h (± 10 min), 3 h (± 10 min), 4 h (± 15 min), 6 h (± 15 min), 8 h (± 15 min), 12 h (± 60 min), 24 h (± 120 min) and 48 h (± 120 min; Day -7 to Day -3 admission only) post-dose. The same C2D1 sampling schedule will be used for patients that are dose escalated on C2D1 of the increased dose
k) Monthly follow-up only required for those AEs and SAEs considered drug-related (highly probably, probably, or possible) that are present at time patient ends the study. Monthly follow-up to continue until resolution to baseline, stabilisation or patient starts another anticancer treatment.

Table 15: Schedule of events- Dose expansion stage

Observation/Investigation	**Pre-study**		**Standard evaluations for each cycle of CCT3833; 1 cycle = 28 days**				**Off study**	**Follow up (for AE until resolution)**
	Between Day -28 and Cycle 1	**Between Day -7 and Cycle 1**	**Cycle 1, Day 1 (± 1day)**	**Day 15 (± 1day)**	**Cycle 2, Day 1 (± 1day)**	**Monthly thereafter if no DLT observed (± 1day)**	**(± 3 days)**	**Monthly**
Written informed consent	x							
Demographics and height	x							
Medical history	x							
Availability of historical tumour biopsy	x							
Radiological assessment[A]	x		At end of every 2 cycles				x	
Clinical disease assessment (if applicable)		x	At end of every cycle				x	
AE evaluation	x		x	x	x	x	x	x[I]
Concurrent medications	x		x	x	x	x	x	
Urinalysis (bHCG)[B]		x						
Tumour serum markers (if applicable)		x	At end of every cycle				x (unless performed within previous 6 weeks)	
Optional tumour biopsy[C]	x				x		x	
Optional CTC/genetics research blood samples[D]	x				x (and every 2 cycles thereafter)		x	
ECOG performance status (Appendix 2)	x	x	x	x	x	x	x	
Physical examination[E]		x	x	x	x	x	x	
Weight		x	x		x	x	x	
Vital signs[F]: temperature, pulse, BP, oxygen saturation		x	x	x	x	x	x	
Laboratory tests[G]		x	x	x	x	x	x	x[I]

ECG		x	x	x	x	x	x	
Echocardiogram[H] (±3 days)	x				x			

A. Radiological assessment using CT or MRI as appropriate. Baseline assessment to include MRI brain; only to be repeated if evidence of brain metastases at baseline or in response to new symptoms.
B. If the patient is a woman of child bearing potential
C. Tumour tissue needle biopsies (10mg material required) for pharmacodynamics assessment will be optional for patients treated in Part B (expansion cohorts). The three sampling points will be pre-dose between Day -28 and C1D1, during treatment on C2D1 (± 3 days), and at disease progression.
D. Research blood samples for circulating tumour cell collection (2-3 x 10mL) will be requested (optional) from patients in Part B (dose expansion stage). The sampling points will be pre-dose between Day -28 and Cycle 1, day 1, at Cycle 2 Day 1 (±3 days), and every 2 cycles thereafter (i.e. Cycle 4 day 1, Cycle 6 day 1 etc) and when the patient is withdrawn from treatment.
E. Complete physical examination to be performed pre-study, then all examinations can be symptom-directed performed on Day 1 of each cycle
F. Temperature, pulse rate, blood pressure and oxygen saturation rate should be performed at each clinical visit.
G. Laboratory tests will be performed alongside each clinical visit; clinical laboratory assessments should therefore be performed on Days 1, and 15 during Cycle 1 and then reduced to once a month (pre-dose on Day 1) from Cycle 2 onwards. In the event of a grade 4 neutropenia or grade 4 thrombocytopenia, a full blood count must be performed at least on Day 5 after the onset of the event to determine if a DLT has occurred. Continue close monitoring until resolution to grade 3 or less. Non fasting glucose and LDH are required for biochemistry. If non fasting glucose >7.8 mmol/l, repeat as a fasting glucose. If this too demonstrates grade 3 hyperglycaemia, a formal glucose tolerance test should be undertaken, and appropriate management of hyperglycaemia initiated.
H. An echocardiogram will be performed pre-study and at the start of Cycle 2 (±3 days). It will then only be repeated as clinically indicated.
I. Monthly follow-up only required for those AEs and SAEs considered drug-related (highly probably, probably, or possible) that are present at time patient ends the study. Monthly follow-up to continue until resolution to baseline, stabilisation or patient starts another anticancer treatment.

9 ASSESSMENT OF SAFETY

9.1 Adverse event definitions

9.1.1 Adverse events

An adverse event (AE) is any untoward, undesired or unplanned occurrence in a patient administered an IMP, a comparator product or an approved drug. An AE can be a sign, symptom, disease, and/or laboratory or physiological observation that may or may not be related to the CCT3833 or comparator.

An AE includes but is not limited to those in the following list:

- A clinically significant worsening of a pre-existing condition. This includes conditions that may resolve completely and then become abnormal again.
- AEs occurring from an overdose of an IMP, whether accidental or intentional.
- AEs occurring from lack of efficacy of an IMP, for example, if the Investigator suspects that a drug batch is not efficacious or if the Investigator suspects that the IMP has contributed to disease progression.

Other reportable events that must be treated as AEs are listed below:

- Pregnancy exposure to the IMP. Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within 6 months of the last IMP administration must be reported to the RM-CTU in the same timelines as an SAE. These should be reported even if the patient is withdrawn from the trial.
- Overdose or inadvertent or accidental exposure to an IMP with or without an AE
- Any AE that could be related to the protocol procedures, and which could modify the conduct of the trial.

Underlying disease - Any event(s) considered related to the underlying disease do not require reporting.

9.1.2 Serious adverse events

A serious adverse event (SAE) is any AE, regardless of dose, causality or expectedness, that:

- results in death.
- is life-threatening.
- requires in-patient hospitalisation or prolongs existing in-patient hospitalisation (some hospitalisations are exempt from SAE reporting – see section 9.2.1).
- results in persistent or significant incapacity or disability.
- is a congenital anomaly or birth defect.
- is any other medically important event.

For screening failures, SAEs will be reported to the RM-CTU from the date of consent until the date the patient is confirmed as ineligible. For eligible patients, SAE and AE collection and monitoring commences from the time the patient gives their written consent to participate in the trial and continues for 28 days after the last administration of the IMP.

Follow-up of AEs with a causality of possibly, probably or highly probably related to the IMP will continue until the events resolve, stabilise or the patient starts another anti-cancer therapy.

9.1.3 Determining adverse event causality

The relationship of an AE to the IMP is determined as follows:

Highly probable

- Starts within a time related to the IMP administration and
- No obvious alternative medical explanation.

Probable

- Starts within a time related to the IMP administration and
- Cannot be reasonably explained by known characteristics of the patient's clinical state.

Possible

- Starts within a time related to the IMP administration and
- A causal relationship between the IMP and the AE is at least a reasonable possibility.

Unlikely

- The time association or the patient's clinical state is such that the trial drug is not likely to have had an association with the observed effect.

Not related

- The AE is definitely not associated with the IMP administration.

Note: Drug-related refers to events assessed as possible, probable, highly probable or definitely.

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP, other illness, progressive malignancy etc) and must provide his/her opinion of the causal relationship between each AE and IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

9.1.4 Expectedness

Assessment of expectedness will be made by the Investigator against the current version of the Investigator Brochure. If updated versions of the Investigator's Brochure are released during the course of the trial then assessment of expectedness will be made against the updated version.

9.1.5 Suspected, unexpected, serious, adverse reactions (SUSAR)

A SUSAR is a suspected, unexpected, serious adverse reaction. All AEs and SAEs will be assessed for seriousness, causality and expectedness. An SAE will be considered to be a

SUSAR if it is possibly, probably or definitely related to CTC3833 and has not previously been reported. The Investigator and study team will rapidly report all SUSARs to the RM-CTU within 24 hours of becoming aware of the event. The RM-CTU will ensure that the Sponsor, the MHRA and main REC are notified within the timelines specified in legislation (SI 2004/1031 as amended).

9.2 Expedited reporting of SAEs

All SAEs, regardless of causality, must be reported to RM-CTU within 24 hours of knowledge of the event. SAEs should be documented on an SAE report form.

This form should be sent to:
Email: panRAF@rmh.nhs.uk
Fax: 020 8915 6762

Each episode of an SAE must be recorded on a separate SAE report form. The NCI CTCAE v4.03 (Appendix 4) must be used to grade each SAE, and the worst grade recorded. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the RM-CTU on a new SAE report form. If the SAE has not been reported within the specified timeframes, a reason for lateness must be included when sending the SAE report form. Should the Investigator become aware of any drug-related SAEs after the patient goes 'off study', these must also be reported within the specified timelines above.

9.2.1 Events exempt from being reported as SAEs

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the case report form (eCRF).

Underlying disease - Any events considered related to the underlying disease, such as disease progression, do not require SAE reporting.

Elective admissions

Elective admissions to hospital for procedures which were planned and documented in the medical records at the time of consent are not SAEs, and do not require SAE reporting. Hospitalisation for administration of the IMP, or to facilitate study procedures such as pharmacokinetic sampling according to the trial protocol is also exempt from being reported as an SAE.

9.3 Recording of AEs and SAEs in eCRFs

All AEs, including SAEs, must be recorded in the eCRF for eligible patients. All concomitant medications, including herbal medications and supplements must be recorded. Any therapy used to treat the event must be recorded. The eCRF will be reconciled with the safety database during and at the end of the trial. Therefore, the sites should ensure the data entered on the SAE report form and the data entered into the eCRF are consistent. The SRC and the Investigator(s) will regularly review the safety data.

9.4 Follow-up of AEs

Follow-up will continue until all the necessary safety data for the event has been gathered and until the drug-related AE or SAE has either resolved, returned to baseline or stabilised, or the patient has received further anti-cancer therapy. Requested follow-up information should be reported to the RM-CTU in a timely manner and as soon as possible after receipt of the follow-up request. For fatal or life-threatening cases, follow-up information should be reported as soon as possible

9.5 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazards to their health or safety.

USMs may be taken without prior authorisation from the competent authority.

The Medicines and Healthcare products Regulations Agency (MHRA) and the Research Ethics Committee (REC) must be notified immediately and in any event within 3 days. Both parties will be notified by telephone immediately and in writing within 3 days of such measures being taken.

Should the site initiate a USM, the Investigator must inform the Sponsor immediately either by:

Email: panRAF@rmh.nhs.uk
Telephone: 020 8642 6503
Fax: 020 8915 6762

The notification must include:

- The date of the USM;
- Who took the decision; and
- Why the action was taken.

The Sponsor will then notify the MHRA and main REC within 3 days of the USM initiation. The Sponsor will distribute the response and any subsequent amendments to the trial sites.

CI Contact Details:

Name: Dr. James Larkin
Address: Renal and Melanoma Unit
The Royal Marsden NHS Foundation Trust
203 Fulham Road
London SW3 6JJ
Tel: 020 7811 8576
Fax: 020 7811 8103

9.6 Pregnancy

The Investigator must make every effort to try and ensure that a clinical trial patient or their partner does not become pregnant during the trial or for 6 months afterwards. This should

be done and documented as part of the consent process by explaining clearly to the patient the potential dangers of becoming pregnant and also providing each patient with information about appropriate medically approved contraception. Two forms of medically approved contraception should be used, such as:

- Oral contraceptive and condom
- Intra-uterine device and condom
- Diaphragms with spermicidal gel and condom

Contraceptives should be used for 4 weeks before the patient joins the trial, throughout the trial and for 6 months after completing the trial.

It should be explained to male patients that if his partner is able to become pregnant, is pregnant or breast feeding when he enters the trial, he should use barrier methods of contraception (condom plus spermicidal gel) to prevent exposure to the IMP. However, if a patient or a partner of a patient does become pregnant the reporting procedures below must be followed:

Any pregnancy occurring in a patient or a patient's partner during treatment or within 6 months of the last IMP administration must be reported within 24 h of the site staff becoming aware of it using a Pregnancy Notification Form. It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner. The pregnancy outcome must be reported to RM-CTU, using a Pregnancy Outcome Form.

The Investigator must ensure that all patients are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with the IMP and occurring up to 6 months after the last IMP administration. The Investigator should offer counselling to the patient and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient and the baby should continue until the conclusion of the pregnancy, if the patient or patient's partner has consented to this.

9.6.1 Other definitions of outcome

Toxic death: Any death to which drug toxicity is thought to have a major contribution.

Early death: Death during the first 28 days of treatment.

10 DATA ANALYSIS AND STATISTICAL CONSIDERATION

10.1 General considerations

This is an open-label, dose-escalating, non-randomised, multi-centre Phase 1 study of continuous once daily oral administration of CCT3833 as a single agent. The study will proceed in two separate parts. In Part A, dose escalation will proceed to establish MTD, pharmacokinetic data and relate this to pharmacodynamics data from tumour tissues, using a rolling six design. In Part B, the population will be enriched for melanoma patients, with BRAF or RAS mutations. Patients enrolled in Parts A and B will continue until toxicity, disease progression, or the meeting of an alternative withdrawal criterion.

10.2 Sample size

The sample size for this Phase 1 trial is not based on a formal sample size calculation as no formal statistical hypothesis is being tested. The total number of patients has been based on the desire to obtain adequate tolerability, safety, pharmacokinetic and pharmacodynamics data while exposing as few patients as possible to the IMP and procedures. The total number of patients required will depend upon the toxicities encountered and the number of dose cohorts required.

In Part A, the minimum number of patients will be 3, if there are 2 DLTs at the starting dose. The maximum number of patients is expected to be 42.

In Part B, there are 3 different patient cohorts each including 9 recruited patients, leading to a maximum of 27 patients within the expansion phase. An additional small number of patients from Part A may continue on treatment into Part B if they meet the inclusion criteria. These patients will be in addition to the 27 new patients recruited to Part B.

10.3 Statistical analysis

All quantitative data will be presented as number of observations, mean, standard deviation, minimum and maximum values. Qualitative data will be presented as number of observations and percentages. When appropriate, data will be presented together with 95% confidence intervals.

Baseline characteristics will be summarised for all enrolled patients. Patients who died or withdrew before treatment started or did not complete the required safety observations will be described and evaluated separately. Treatment administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of therapy will be described.

The trial aims to determine the following endpoints:

Primary:

a. Establishing the MTD and RP2D of CCT3833 (Part A only)
b. Assess the safety and tolerability profile of CCT3833 (Part A and B)

Secondary:

a. Establish pharmacokinetic parameters using the plasma levels of CCT3833 (Part A only)
b. Measure response using radiological/clinical criteria (Part A and B)
c. Determine the correlation between pharmacokinetic parameters and tolerability (Part A only)

Exploratory:

a. Measurement of pharmacodynamics biomarkers (Parts A and B)
b. Determine the magnitude and duration of effect of PD biomarkers (Parts A and B)

10.3.1 Safety and toxicity:

Safety data will be collected from the date of written consent. Safety variables will be summarised by descriptive statistics. The number and percentage of patients experiencing DLT or non-DLT toxicity in each dose level will be tabulated and the number of cohorts recruited in Part A will be recorded, respectively. AEs will be coded using MedDRA and reported for each dose level and presented as tables of frequency of AEs by body system and by worst severity grade observed. Tables should indicate related and unrelated events. The number and percentage of toxicity grades 1-4 and grade 3-4 respectively, experienced by those patients recruited in Part B will be reported. Laboratory data will be presented by dose level at each observation time. Values outside normal limits will be identified and summarised by frequency distribution.

10.3.2 Pharmacodynamics

PD data will be analysed as appropriate depending on the biomarker being studied and the assay employed.

10.3.3 Pharmacokinetics

PK parameters will be derived from sample data, including peak plasma concentration (C_{max}), time to reach C_{max} (T_{max}), elimination half-life ($T_{1/2}$), area under the curve from zero to the time of last quantifiable concentration (AUC_{0-t}) and AUC extrapolated to infinite time (AUC_{∞}). In addition, comparison between single dose and multi-dose PK parameters will be made for assessment of steady-state drug accumulation.

Bioanalysis will be performed by Covance UK**.** PK samples will be analysed for all patients in Part A, with a minimum of 2 patients/cohort analysis available to inform the assessment of patient safety and dose reviews.

The Correlation between the PK parameters derived and DLT or non-DLT toxicity at each dose level. Calculation of a correlation coefficient will determine the significance.

10.3.4 Response evaluation:

The best tumour response evaluation as determined radiologically or clinically will be presented as proportions. Part A and B patients undergo response assessment every 8 weeks (2 cycles), the first response assessment is therefore at 8 weeks, and they continue after that at 8 weekly intervals unless there is clinically measurable progression or toxicity. The association of the pharmacodynamics biomarkers with treatment response will be explored.

10.3.5 Expansion cohorts (Part B):

The tolerability, PD parameters and tumour response data will be evaluated as stated above for each melanoma cohort separately.

10.4 Timing of analyses

Toxicity data will be reviewed by the SRC prior to any decision regarding dose escalation or opening of new dose cohorts.

The final analysis will be conducted after one of the following conditions is met:

- The study is terminated early (for example, due to toxicity).
- All patients have had the opportunity to receive 12 cycles of treatment and are either continuing with treatment or have completed their 'Off-study' visit (i.e. 14 days (± 7 days) after the last dose of CCT3833).
- N.B. All patients are allowed to continue with CCT3833 treatment beyond 12 cycles if they are receiving therapeutic benefit.

Once one of the conditions is met, a data cut-off date will be established. All patient visits occurring on or before this date will be analysed and summarised in the final clinical study report. Any data collected after this date will be summarised in a supplemental report.

11 ADMINISTRATION AND RESEARCH GOVERNANCE

This trial will be conducted under a clinical trial authorisation (CTA). Approval from the Medicines and Healthcare products Regulation Agency (MHRA) and the relevant Research Ethics Committees will be obtained before the start of this trial. This trial is co-sponsored by the Royal Marsden NHS Foundation Trust and the Institute Of Cancer Research. Applicable regulatory requirements are described in this section.

11.1 Protocol deviations and amendments

Amendments to the protocol may only be made with the approval of the Sponsor, CI, site PIs and statistician. A protocol amendment will be subject to review by the Sponsor before obtaining relevant approvals. Ethics Committee favourable opinion (and MHRA approval if appropriate) will be obtained by the CI before the amendment can be distributed to sites and implemented.

11.2 Completion of the electronic case report form

The Investigators are responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the eCRFs.

Only the Investigator and those personnel who have completed the Study Team Responsibilities Delegation Log as authorised by the PI, should enter or change data in the eCRFs. All protocol required investigations must be reported in the eCRF. The Investigators must retain all original reports, traces and images from these investigations for future reference. The data will be entered in a clinical trials database (Macro V4).

The eCRF will be signed electronically by the Investigator or by an authorised staff member. Study specific information will be entered into an eCRF on a regular basis (ideally after each patient visit). Data that are derived should be consistent with the source documents or the discrepancies should be explained. All eCRF data should be anonymous, ie identified by study patient number only.

Once data has been entered by the site personnel on the eCRF, the data will be reviewed and checked for error and inconsistencies by data management staff at the CTU.

Once the patient is 'off study' and the eCRF has been fully completed, the Investigator must provide a signature to authorise the complete subject data.

11.3 Trial performance and monitoring

11.3.1 Management of the study

The RM-CTU will be responsible for the day to day coordination and management of the trial. This includes all duties relating to pharmacovigilance in accordance with section 9 . The RM-CTU will act as custodian of the eCRF data on behalf of the Sponsor.

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial centres. RM-CTU must be informed immediately of any change in the personnel involved in the conduct of the trial.

During the trial the RM-CTU is responsible for monitoring data quality in accordance with relevant standard operating procedures (SOPs). Before the trial start, the Investigator will be advised of the anticipated frequency of the monitoring visits. The Investigator will receive reasonable notification before each monitoring visit.

It is the responsibility of the Sponsor to

- Review trial records and compare them with source documents
- Check pharmacodynamic samples and storage
- Discuss the conduct of the trial and any emerging problems with the Investigator
- Check that the drug storage, dispensing and retrieval are reliable and appropriate, and
- Verify that the available facilities remain acceptable.

All unused drug supplied must be returned to the supplier or destroyed at the Investigator site by an authorised person who will provide signed confirmation of destruction.

It is the responsibility of the Sponsor to inform the REC within 90 days of the 'end of the trial' (i.e. last patient study visit) that the trial has closed.

11.3.2 Source document verification

Unless agreed in writing, all data collected in the eCRF must be verifiable by the source data. Therefore it is the Investigator's responsibility to ensure that all relevant data is clearly recorded in the medical records. The Investigator must allow the RM-CTU direct access to relevant source documentation for verification of data entered into the eCRF, taking into account data protection regulations. Entries in the eCRF will be compared with patients' medical records and trial source data using a risk-based approach and the verification will be documented in the monitoring report.

The patients' medical records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the Sponsor appointed to audit the trial, and by REC and regulatory authorities. The Sponsor and its representatives may look at and analyse patients confidential medical information in any country worldwide. Details will remain confidential and patients' names will not be recorded outside the hospital.

11.3.3 Clinical study report

At appropriate intervals, including for the purpose of dose escalation decisions, interim data listings will be prepared to give the Investigator and analysing laboratories the possibility to review the data and check the completeness of information collected. The dose escalation stage of the trial is expected to take approximately 18 months to establish the MTD. It is anticipated that a trial report will be generated after approximately 24 months to describe initial safety data and any early efficacy signal. The dose expansion stage is expected to take 24 months to complete. During this stage, reports will be generated on a quarterly basis. These will outline patient demographics, and describe emerging toxicity and efficacy data.

All clinical data will be presented at the end of the study on final data listings. The CI, along with the Sponsor-appointed statistician will prepare a clinical study report based on the final data listings. The report will be submitted to the Investigator(s) for review. A summary of the final clinical report must be provided to the MHRA and to the Research Ethics Committee. These results may also be made available to commercial third parties.

11.3.4 Record retention

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified. These essential documents (as detailed in Chapter V of Volume 10 (Clinical Trials) of The Rules Governing Medicinal Products in the European Union based upon Section 8 of the ICH GCP Guidelines), including source documents such as scans, trial related documents and copies of the eCRFs, associated audit trail and SAE report forms, shall show whether the Investigator has complied with the principles and guidelines of Good Clinical Practice (GCP).

All essential documents required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for the minimum period required by national legislation. Records must not be destroyed without prior written approval from the Sponsor.

The medical files of trial patients shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

11.3.5 Ethical considerations

The Trial will be conducted in accordance with the ethical principles founded in the Declaration of Helsinki (2013, Appendix 1). Before starting the trial, the protocol, patient information sheet and consent form must be approved by a Research Ethics Committee and to the relevant regulatory authorities.

It is the Chief/Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The

Chief/Principal Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented, where appropriate.

11.3.6 Risk mitigation

Although panRAF inhibition is not an established therapeutic strategy, the targeting and inhibition of intracellular kinases and in particular BRAF targeting has been extensively studied both experimentally and clinically. RAF kinases therefore represent a validated therapeutic target (particular in melanoma where disease pathogenesis is highly dependent on the aberrant function of the MAPK pathway via these kinases) that warrants further clinical investigation.

This trial does not represent a 'first in class' project, as the extensive experimental and clinical experience of kinase inhibitors (such as sorafenib) and BRAF inhibitors (such as vemurafenib) can be drawn upon to predict potential risks due to panRAF inhibition and to allow planning to mitigate these anticipated risks associated with panRAF inhibition.

As a 'first in man' trial, patient safety is of paramount concern during this trial. Whilst all aspects of the trial have been designed with patient safety in mind, the following design aspects have been incorporated to ensure that (particularly during all dose escalation stages) an individual patient's risk is minimised:

- Each patient will have a single dose 'run-in' 3-7 days prior to commencement of continuous dosing
- Patients will be admitted for observation and PK assessments for 48 hours after 1st dose administration of the continuous dosing i.e. Cycle 1 Day 1
- One patient will commence a dose cohort, with at least 7 days delay between the first and any subsequent patients being dosed within that cohort
- All emerging toxicities will be reviewed and graded in real time
- Decisions to dose escalate will be made by a panel of clinicians, including an independent chair and other independent physicians, to ensure independence and safety

The toxic effects (and associated risks) relating to the panRAF inhibitor therapy are not yet established. Unknown risks will be mitigated against with the usual comprehensive approach to clinical observation and routine investigation/assessment that is required in any clinical trial. panRAF inhibitor therapy may induce toxic effects similar to those seen with RAF or other kinase inhibitors. These potential risks will be mitigated against with the specific steps as outlined in Table 16.

Table 16: Mitigation of potential risks

Potential Risk	Mitigating Steps in Trial
Skin reactions /malignancies	Regular scheduled clinical review and examination (including palms and soles) with referral for dermatology review/treatment of lesions.
Arthralgia	Regular scheduled clinical review and examination.

Myositis	Regular scheduled clinical review and examination; monitoring of blood tests (e.g., CK); referral for further specialist review as necessary.
Alopecia	Regular scheduled clinical review and examination.
Fatigue	Regular scheduled clinical review and examination.
Uveitis/Iritis	Regular scheduled clinical review and examination with referral to Ophthalmology for review of any concerning symptoms.
Vasospasm	Regular scheduled clinical review and examination with referral for further specialist review as necessary.
Slow wound healing	Patients requiring major surgery to be excluded from trial.
Febrile reactions	Clinical observations including temperature measurement.
Haematological abnormalities such as anaemia or thrombocytopenia	Routine haematology blood test monitoring.
Biochemical abnormalities such as altered liver function tests	Routine biochemistry blood test monitoring.
ECG changes eg QTc prolongation	Exclusion of patients with baseline QTc prolongation (> 450 ms). Exclusion of patients with uncontrolled hypertension on > 1 antihypertensive. ECG monitoring of patients during treatment and central analysis of ECGs for any effects on QTc interval, and exclusion of patients if QTc interval becomes > 500 ms.
Left ventricular dysfunction (eg reduced LVEF)	Baseline echocardiography to exclude patients with inadequate LVEF (< 50%). Repeat monitoring with echo at 1 month and thereafter if symptoms of dysfunction develop.
Embryo-fœtal toxicity	Measures to avoid pregnancy as described in section 9.6.
Any signal emerging during clinical study	Ongoing monitoring by the SRC.

11.3.7 Regulatory compliance

The Sponsor and Chief/Principal Investigator must ensure that the trial is carried out in accordance with all the laws and statutes, as amended from time to time, applicable to the performance of Clinical Trials, including but not limited to the principles of ICH Harmonised Tripartite Guideline for GCP (CPMP/ICH/135/95) as set out in schedule 1 (Conditions and Principles of GCP for the protection of clinical trial subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 (S.I 1031) and the GCP Directive 2005/28/EC as set out in the amended regulations 2006 (S.I 1928).

11.3.8 Notifications of serious breaches to GCP and/or the protocol

The Sponsor will notify the MHRA and REC in writing of any serious breaches of:

a. The condition and principles of GCP in connection with the trial.
b. The protocol.

This will be done within 7 days if becoming aware of that breach, in accordance with the applicable UK regulations as amended from time to time.

For the Purpose of the regulations a "serious breach" is a breach which is likely to effect to a significant degree

a. The safety or physical integrity of the subjects of the trial; or
b. The scientific integrity of the trial.

Systematic or persistent non-compliance by the site with GCP and/or the study protocol, including failure to report SAEs occurring on trial within the specified timeframes, may be deemed a serious breach.

11.3.9 Indemnity

The Co-Sponsors are responsible for harm arising from the experimental treatment given to patients recruited to this study.

Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements for clinical negligence. A copy of the relevant insurance policy/indemnity scheme or summary shall be provided to the Co-Sponsors on request.

ICR has in force a no-fault compensation insurance for injury caused to patients participating in this clinical trial. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to ICR's insurers.

The Co-Sponsors have secured an indemnity from the dose formulation manufacturer in respect of injury caused to patients as a result of manufacturing defects.

11.3.10 NHS indemnity statement

The Royal Marsden Hospital is able to provide insurance to cover liabilities and prospective liabilities arising from negligent harm however the Royal Marsden Hospital cannot provide insurance over claims arising from non-negligent harm. Where studies are carried out in a hospital, the hospital continues to have its duty of care to the patient being treated in that hospital, and, except in the case of the Royal Marsden, the Co-Sponsors do not accept liability for negligence on the part of employees at hospitals and cannot be held liable for any breach in the hospitals duty of care.

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.

11.4 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, 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.

11.5 Publication policy and press releases

The trial results will be submitted for publication in a relevant medical journal with authorship according to the criteria defined by the ICMJE (http://www.icmje.org). These state that: Authorship credit should be based 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Draft publications (manuscripts, abstracts, slides and posters) should be submitted to the RM-CTU for circulation to the relevant parties to allow sufficient time for review prior to submission.

There will be a twenty five (25) business day period to review all publications and respond to the author with any revisions.

A delay in publication may be requested by the Wellcome Trust for a maximum of 40 business days to allow for patent filing (if appropriate). Alternatively a maximum delay of 12 months may be requested so as not to materially jeopardise any explorational activity being carried out (if applicable).

All publications relating to the trial will be deposited into PubMedCentral or UK PubMedCentral upon acceptance for publication and made freely available as soon as possible and in any event no later than six months after the official date of final publication. The trial will be registered on ClinicalTrials.gov, on the International Standard Randomised Controlled Trial Number Register (ISRCTN), or on another register listed on the WHO International Clinical Trials Registry Platform (ICTRP).

11.6 Funding

The study is co-sponsored by the Royal Marsden NHS Foundation Trust and the Institute Of Cancer Research. The study is funded through a grant from the NIHR Royal Marsden and the Institute Of Cancer Research Biomedical Research Centre. The preclinical and drug development work has been supported by a grant from the Wellcome Trust.

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13 APPENDICES

Appendix 1: Declaration of Helsinki

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 DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

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 be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. 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.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. 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 proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must 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.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this 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.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

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

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. 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.

22. The design and performance of each research study involving human subjects must be clearly described and justified 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, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. 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 SAEs. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, 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, post-study provisions 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.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must 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 must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised 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 group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent 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 authorised representative. The potential subject's dissent should be respected.
30. 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 group. In such circumstances the physician must seek informed consent from the legally authorised 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 must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their 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 adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

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

    - Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
    - Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
      Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, Sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, Sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers 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. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

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

Appendix 2: ECOG performance scale

The ECOG performance status classification categorises patients as:

0: able to carry out all normal activity without restriction

1: restricted in strenuous activity but ambulatory and able to carry out light work

2: ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours

3: symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden

4: completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Appendix 3: List of disallowed concomitant medications

Potent inhibitors of CYP3A4:

boceprevir	itraconazole	ritonavir
clarithromycin	ketoconazole	saquinavir
conivaptan	lopinavir/ RIT	telaprevir
elvitegravir/ RIT	mibefradil	telithromycin
fluconazole	nefazodone	tipranavir/RIT
grapefruit juice*	nelfinavir	troleandomycin
indinavir	posaconazole	voriconazole

For patients taking any of the above, the required wash-out period prior to starting CCT3833 is 2 weeks.

*Grapefruit: Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g., grapefruit juice or marmalade) during the study (e.g., no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1-2 teaspoons (15 g) of Seville orange marmalade daily.

Potent inducers of CYP3A4:

avasimibe	nevirapine	rifampin
carbamazepine	phenobarbital	St John's Wort
enzalutamide	phenytoin	
mitotane	rifabutin	

Potent inhibitors of CYP2C8:
gemfibrozil

Inducers if CYP2C8:

rifampicin
carbamazepine
phenobarbital
rifabutin

Others:

warfarin

Appendix 4: Common Terminology Criteria for Adverse Events Version 4

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 for toxicity and Serious Adverse Event reporting.

A copy of the CTCAE v4.03 can be downloaded from the NCI home page http://evs.nci.nih.gov/ftp1/CTCAE/About.html

All appropriate treatment areas should have access to a copy of the CTCAE v4.03.

Appendix 5: Revised Response Evaluation Criteria In Solid Tumours (RECIST) Guideline (version 1.1)

[Eisenhauer, 2009]

Baseline documentation of target and non-target lesions

All baseline lesion assessments must be performed within 28 days of randomizations.

Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.

Pathological lymph nodes with <15mm and but 10mm short axis are considered non measurable.

Pathological lymph nodes with 15mm short axis are considered measurable and can be selected as target lesions, however lymph nodes should not be selected as target lesions when other suitable target lesions are available.

Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.

All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Efficacy assessment

Disease progression and response evaluations will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Eisenhauer, 2009].

See the Schedule of events Tables 13 and 14 (Section 8.1 and 8.2) for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post baseline assessments, a window of 3 days is permitted to allow for flexible scheduling.

In Part A, the following are required at baseline: CT for Chest/Abdomen/Pelvis or MRI for Abdomen/Pelvis and clinical disease assessment for palpable lesions. At each post baseline

assessment, evaluations of the sites of disease identified by these scans are required.. Brain and Bone scans should be performed as clinically indicated. In Part B, brain scans are additionally required at baseline, and thereafter at each post baseline assessment only if brain disease is detected at baseline.

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed no less than 4 weeks after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol-scheduled evaluation is still required (e.g. evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments).

A baseline brain scan is required for all subjects in Part B only. For subjects without CNS disease at baseline, subsequent brain scans should only be performed as clinically indicated (e.g. symptoms suggestive of CNS progression). For subjects with CNS disease at baseline, a brain scan is required as clinically indicated. All subjects with melanoma should have a baseline brain scan at screening. In addition, in order to confirm a CR in a subject with brain disease at baseline, a brain scan must be performed 1 week prior to the 1st set of images showing CR to 4 weeks after the next protocol specified assessment.

Assessment guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion.
- All measurements should be taken and recorded in millimetres (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the eCRF.
- Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules). In the case of skin lesions, documentation by colour photography, including a ruler/callipers to measure the size of the lesion, is required. [Eisenhauer, 2009].

- CT and MRI: Contrast enhanced CT with 5mm contiguous slices is recommended.
- Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used. [Eisenhauer, 2009].
- X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Eisenhauer, 2009].
- Brain Scan: Baseline brain scans are required in Part B of the study, then contrast enhanced MRI is preferable to contrast enhanced CT.
- Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e., X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

Guidelines for evaluation of disease

Measurable and non-measurable definitions

Measurable lesion:

- A non nodal lesion that can be accurately measured in at least one dimension (longest dimension) of 10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be 20 mm).
- 10 mm calliper/ruler measurement by clinical exam or medical photography.
- 20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if 15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

Non-measurable lesion:

- All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement

of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

- Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.
- Non-Measurable only disease: The presence of only non-measurable lesions. Note: non-measurable only disease is not allowed per protocol.

Response criteria

Evaluation of target lesions

Definitions for assessment of response for target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PrD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note: If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.

If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PrD cannot be made, the response assessment should be NE.

All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g.2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PrD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).
- Non-CR/Non-PrD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.
- Progressive Disease (PrD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note: In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.

Sites of non-target lesions, which are not assessed at a particular time point based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the Investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

Evaluation of overall response

Table i presents the overall response at an individual time point for all possible combinations of tumour responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table i: Evaluation of overall response for subjects with measurable disease at baseline

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR or NA	No	CR
CR	Non-CR/Non-PrD or NE	No	PR
PR	Non-PrD or NA or NE	No	PR

SD	Non-PrD or NA or NE	No	SD
NE	Non-PrD or NA or NE	No	NE
PrD	Any	Yes or No	PrD
Any	PrD	Yes or No	PrD
Any	Any	Yes	PrD

CR=complete response, PR = partial response, SD=stable disease, PrD=progressive disease, NA= not applicable, and NE=not evaluable

Note: Subjects 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." Objective response status is determined by evaluations of disease burden. 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 CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically by GSK based on the Investigators assessment of response at each time point.

To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 4 weeks.

If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PrD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PrD. Alternative subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

Confirmation criteria (recommended):

To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.