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ORIGINAL ARTICLE

A two-part Phase II study of cediranib in patients with advanced solid tumours: the effect of food on single-dose pharmacokinetics and an evaluation of safety, efficacy and imaging pharmacodynamics

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Abstract
Background Cediranib (RECENTIN™) is an oral, highly potent VEGF inhibitor. This study evaluated the effect of food on the pharmacokinetics of cediranib and compared the administration of continual cediranib via two dosing strategies using this as a platform to investigate pharmacodynamic imaging biomarkers.
Methods Sixty patients were randomised to receive two single doses of cediranib in either fed/fasted or fasted/fed state (Part A). In continual dosage phase (Part B), patients were randomised to a fixed-dose or dose-escalation arm. Exploratory pharmacodynamic assessments were performed using DCE-MRI and CT enhancing fraction (EnF).
Results In part A, plasma AUC and C_{max} of cediranib were lower in the presence of food by a mean of 24 and 33%, respectively (94% CI: AUC, 12–34% and C_{max}, 20–43%), indicating food reduces cediranib plasma exposure. In part B, cediranib 30 mg/day appeared to be the most sustainable for chronic dosing. Continuous cediranib therapy was associated with sustained antivascular effects up to 16 weeks, with significant reductions in DCE-MRI parameters and CT EnF.
Conclusions It is recommended that cediranib be administered at least 1 h before or 2 h after food. Evidence of antitumour activity was observed, with significant sustained effects upon imaging vascular parameters.

Keywords Cediranib · CT enhancement · DCE-MRI · Food · Pharmacodynamics · Pharmacokinetics

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Introduction

Cediranib (RECENTIN™) is an oral, highly potent tyrosine kinase inhibitor that prevents activation of the vascular endothelial growth factor (VEGF) signalling pathway via VEGF receptors (VEGFR) 1, 2 and 3 [1]. Early clinical data demonstrate that cediranib has antitumour activity across a broad range of tumours both as monotherapy and in combination with certain other agents [2–8]. Common adverse events in these studies included hypertension, diarrhoea and fatigue and these appear to be manageable. In all studies conducted to date, cediranib has been dosed to fasted patients. The primary objectives of this two-part

study (study code 2171L0021) were to compare the pharmacokinetic parameters of cediranib obtained in patients in the fed and fasted state (Part A) and to compare the safety and tolerability of cediranib when given as either a fixed daily dose or an individualised dose-escalation plan (Part B).

An exploratory objective performed at a single participating centre was dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) assessment of tumour microvascular function following cediranib treatment over 4–16 weeks. DCE-MRI has been used in several early phase clinical studies of antiangiogenic agents [9] including cediranib [3] and to assess pharmacodynamic changes following treatment [10, 11]. In this study, DCE-MRI results were compared with those obtained using simple CT enhancement techniques to calculate tumour-enhancing fraction (EnF) [12].

Methods

Study design

Part A was a crossover design in which patients received two single doses of cediranib 45 mg with an 8 days washout period. Patients were randomised 1:1 to receive treatment in either the fed followed by the fasted state or the fasted then the fed state. In the fed period, patients ate a standard high-fat breakfast (as per FDA guidelines) completed 30 min prior to dosing with cediranib. In the fasted state, patients were dosed after an overnight fast (at least 10 h before and 4 h after dosing). Blood samples for pharmacokinetic analyses were collected over 168 h post-dosing on each occasion. The effect of food on the single-dose pharmacokinetics of cediranib was assessed using the criteria for establishing bioequivalence based on the endpoints of AUC and C_{max}. One week after completing the second dose of cediranib, eligible patients could progress to Part B of the study. Patients not entered into Part A could enter into Part B directly, once Part A was complete (Fig. 1a).

In Part B of the study, patients were randomised in a 1:2 ratio to receive daily dosing with cediranib, as either a fixed dose of 45 mg/day or a dose-escalation approach (individualised dosing plan). Patients in either arm could reduce their dose as a result of toxicity. The maximum-tolerated dose (MTD) for each patient was defined as the highest dose for which there was continuous dosing for a period of at least 6 weeks, without dose breaks or interruptions, during the first 16 weeks of treatment. In the individualised dose-escalation arm, patients received an initial dose of cediranib 30 mg/day for 14 days that was increased by 15 mg after each 14-day period, provided treatment was considered tolerable by the investigator. Toxicity assessments and dose increases continued until the MTD or 90 mg (individualised to the patient), whichever was lower. There was a minimum window of 14 days and a maximum window of 28 days between dose-escalations. Treatment continued until withdrawal due to patient request, toxicity or loss of a clinical benefit from continued treatment (Fig. 1b).

This study was approved by a multicentre research ethics committee and by the research governance departments of all participating institutions, and all patients gave written informed consent prior to any study-related procedure.

Eligibility criteria

Eligible patients were those with histologically or cytologically confirmed advanced solid tumours that were refractory to standard therapies or for which no standard therapy existed. All patients were required to have radiologically measurable disease; World Health Organisation performance status 0–2; adequate bone marrow, renal (creatinine clearance $\geq$50 ml/min) and liver function; be able to provide informed consent; and have no contraindications to receiving VEGF inhibitors. Patients were excluded if they had poorly controlled hypertension or other severe or uncontrolled systemic diseases. For participation in the DCE-MRI research component of the study, standard MRI exclusion criteria were employed. Patients were eligible if they had primary or secondary hepatic tumours or tumours at other sites of between 2 and 10 cm in diameter that were deemed assessable by the investigator.

Pharmacokinetic assessments

The primary endpoints of C_{max} and AUC were analysed following single doses of cediranib in both the fed and fasted state. In Part A, blood samples for pharmacokinetic assessments were collected at pre-dose and post-dose at 30 min, 1, 2, 3, 4, 6, 8, 12, 24 and 36 h, and on days 3, 4, 5, 6, 7 and 8. In Part B, blood samples for pharmacokinetic assessments were collected pre-dose and 3 h post-dose every 2 weeks until day 70. All samples were analysed for cediranib by high-performance liquid chromatography with tandem mass spectrometry using a fully validated method. Sample storage stability for up to 6 months at -20°C has been established. The lower limits of quantification were 1 ng/mL in plasma. Pharmacokinetic parameters were calculated by standard non-compartmental methods using WinNonlin software (WinNonlin professional version 5.2) using standard equations.

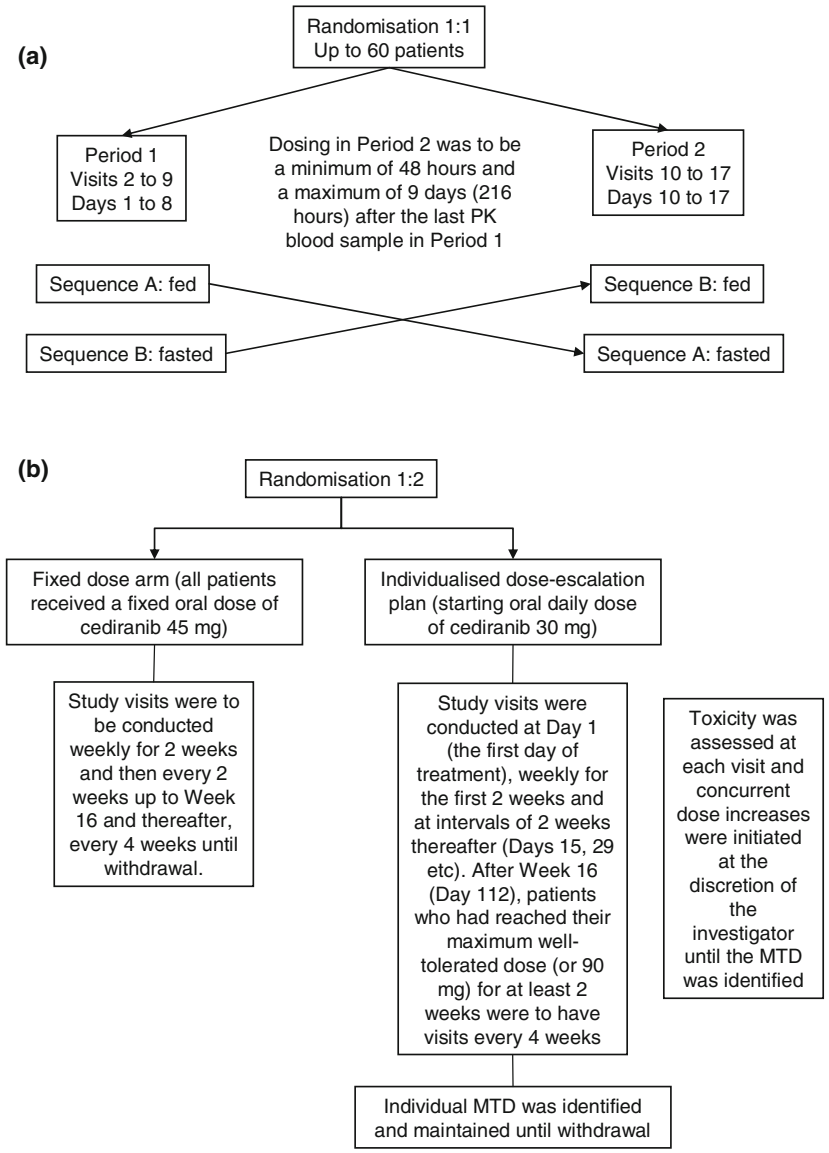

Fig. 1 Study scheme **a** Part A and **b** Part B

Safety and tolerability

Adverse events were recorded throughout the study and graded according to the National Cancer Institute Common Terminology Criteria (CTC) version 3.0.

Electrocardiogram (ECG)

At screening, mean QT with Bazett's correction (QTcB) had to be <470 ms. In Part A of the study, digital ECGs were recorded in triplicate at screening and on day 1 during the fed period of Part A. ECGs were also recorded at pre-dose, on days 1, 2 and 8, and during the fasted period of Part A. The ECG data recorded on day 8 (post-1 week washout, pre-dose) were used as a within-patient control. During Part B of the study, ECGs were recorded at screening (if the patient had not participated in Part A of the study) and at pre-dose and 3 h post-dose on day 1, week 2, week 4 and at the discontinuation visit. In Part A and Part B, assessments of QT were corrected using both Bazett's (QTcB) and Fridericia's formulae (QTcF). A single independent cardiologist, who was blinded to time, treatment and patient identifier, evaluated the digital ECGs centrally.

Efficacy

Tumours were evaluated and categorised according to Response Evaluation Criteria for Solid Tumours (RECIST) determined using anatomical CT scans [13]. Scans were performed prior to Part A, at baseline prior to Part B, at week 8, week 16 and then at 8-week intervals until disease progression.

Pharmacodynamic assessments

At the Christie Hospital NHS site only, the effects of cediranib on vascular parameters were assessed in 10 patients by DCE-MRI. All patients recruited at this site were eligible to voluntarily enter the DCE-MRI component of the study. To assess reproducibility of the parameters, two baseline DCE-MRI scans were performed within a week of each other prior to Part A, with further scans performed in the week prior to starting continuous therapy (Part B) and at weeks 4, 8 and 16. A previously described standard DCE-MRI acquisition protocol was used on a Phillips 1.5T Intera scanner using Omniscan™ contrast agent was employed [14–16]. Whole tumour volumes were selected as regions of interest and defined in 3D manually using the anatomical images by an experienced clinician. Tracer kinetic modelling using the extended Tofts model was applied to each enhancing voxel within the defined whole tumour volume and a median or mean summary value for each parameter was provided for the tumour [17]. To calculate the parameters, arterial input functions (AIF) were either extracted from the imaging data [18] or where a suitable artery was not visible within the field of view or it was not possible to use the vessel for AIF calculation, i.e. due to image artefacts, a previously derived AIF was employed [19]. The model provided estimates of tumour microvascular characteristics, including K^{trans} (trans-capillary contrast agent transfer constant), representing tumour capillary blood flow and permeability, V_e (fractional size of the extracellular extravascular space) and V_p (fractional size of the blood plasma volume). The initial area under the tumour contrast agent–time curve over the first 60 s post-contrast agent arrival ($IAUC_{60}$), a semi-quantitative parameter that reflects the amount of contrast agent delivered and retained in the tumour, was also determined [20].

At each CT RECIST assessment, patients who participated in the DCE-MRI study had their conventional contrast-enhanced CT scans using Omnipaque 300™ contrast agent analysed using an additional CT threshold technique to calculate tumour EnF [12]. CT image analysis was performed using MRIcro software [21] and applied to the same whole tumour volumes used for DCE-MRI analysis. To exclude cystic and calcified areas within the region of interest from analysis, thresholds of <10 HU (Hounsfield units) and >150 HU were applied. The enhancing fraction of the tumour (proportion of enhancing tumour tissues excluding cystic and calcified areas) was determined using four thresholds, 50 HU, 60 HU, 70 HU, and 80 HU to provide an estimate of tumour vascularity.

Statistical analyses

In Part A, food would be considered to have no effect on the pharmacokinetics of cediranib if confidence intervals (CI) for the food effect ratio for the endpoints of AUC and C_{max} of plasma cediranib fell within the acceptance range of 0.8–1.25. The trial was sized to give 90% power with an overall type I error of 5%. As there was little known information on AUC and C_{max}, a planned interim analysis occurred once complete data were available for 12 patients, this determined the group size required ($n = 60$). As the interim analysis was undertaken, 94% CIs were constructed to preserve the overall type I error (using a Pocock alpha spending rule). It would be declared there was no effect of food if the 94% CI fell entirely within 0.8–1.25 for both AUC and C_{max}. Pharmacokinetic parameters from the fed and fasted groups were compared statistically using an analysis of variance (ANOVA) model fitting for the effects of sequence, patients within sequence, period and food (fed/fasted). Patients were eligible for the pharmacokinetic population if they had at least one pharmacokinetic sample, although they may not have been assessable for all of the defined pharmacokinetic parameters. Patients who failed to ingest a significant amount of the breakfast as judged by the investigator were excluded with guidelines provided for assessment.

For the ECG assessments, the formal comparison was conducted by using an analysis of covariance (ANCOVA) model including factors of sequence (fed/fasted or fasted/fed), treatment (test/control arm) and patient within sequence, and baseline as a covariate.

In Part B, the safety outcome variable of exposure to cediranib over 16 weeks was summarised for each patient. Efficacy and pharmacodynamic data were evaluated on an intent-to-treat (ITT) basis. The safety population consisted of all randomised patients who received at least one dose of study medication.

For the DCE-MRI analysis, all available data from the different parts of the study were used. Where multiple lesions were present within a single patient, these were combined into a single measurement for the patient. Whole tumour volume for each patient was the total of the individual volume of lesions; the other DCE-MRI parameters used a geometric mean of lesions within in each patient. For each of the parameters, the percentage change from baseline with associated 95% CI was estimated by using an analysis of covariance (ANCOVA) model including patient as a random effect, visit as a fixed effect and baseline as a covariate. The analysis was based on log-transformed data, and data were then back-transformed prior to calculation of percentages and the associated 95% CIs. The intrapatient variation of MRI parameters was estimated using a mixed-effects linear model including patients that had at least one MRI assessment for reproducibility. The effects of cediranib on MRI parameters were assessed by analysing the reduction in MRI parameters from baseline over the study period up to 16 weeks via a mixed-effects linear model.

CT EnF enhancement data were assessed per scan visit, and non-parametric tests (Wilcoxon signed rank) were used to test for differences between visits from baseline (commencement of Part B) and subsequent visits. To explore the relationship between the CT EnF and DCE-MRI parameters, values were paired for each patient at each visit and non-parametric correlations (Spearman's rank bivariate) were applied.

Results

Patients

Between June 2006 and October 2008, 60 patients were randomised and 54 received at least one dose of study treatment. Five patients remained on study treatment at data cut-off (the date by which all patients had reached week 16 or had withdrawn). Table 1 summarises the baseline demographics and patient characteristics in Parts A and B of the study.

Ten patients from the Christie Hospital NHS site participated in the DCE-MRI component of the study. Three of these patients did not proceed into Part B of the study and therefore only had reproducibility scans performed. Seven patients were scanned during Part B (continual dosage)—two of whom had multiple assessable tumours, leading to a total of eleven tumours assessable by DCE-MRI during the continual administration phase.

Pharmacokinetics

Table 2 summarises the pharmacokinetic parameters following single oral doses of cediranib 45 mg in the fed and fasted states. The primary objective of Part A showed that both the AUC and C_{max} of cediranib were lower in the presence of food by a mean of 24% and 33%, respectively (94% CI: AUC, 12–34% lower and C_{max}, 20–43% lower). The CI for AUC crossed the lower equivalence boundary of 0.8, and the upper boundary of the CI was <1. The CI for C_{max} was entirely outside the equivalence boundary, indicating a clear effect.

Steady-state pharmacokinetics was a secondary objective within part B of the study. High variability of the pharmacokinetic parameters was seen within the population due to significant proportion of the patients undergoing either escalation or de-escalation during the study period.

Safety and tolerability

The mean (standard deviation, SD) dose per day during Part B of the study was 33.79 (9.35) and 31.16 (9.03) mg in

Table 1 Baseline demographics and patient characteristics

	Part A (n = 45)		Part B (n = 47)		Total
	Cediranib 45-mg sequence A fed/fasted (n = 23)	Cediranib 45-mg sequence B fasted/fed (n = 22)	Cediranib 45-mg fixed dose (n = 16)	Cediranib 30- to 90-mg dose-escalation (n = 31)	n = 60
Age, years					
Mean (SD)	58.6 (10.6)	51.2 (14.8)	56.4 (13.1)	56.0 (13.5)	56.0 (13.0)
Range	32–73	19–70	19–73	22–74	19–74
Sex, n					
Male/female	13/10	12/10	8/8	19/12	32/28
Race, n					
Caucasian/oriental	23/0	22/0	16/0	30/1	59/1
Primary tumour location[a]					
Ovary	3 (13.0)	4 (18.2)	2 (12.5)	4 (12.9)	9 (15.0)
Colon	3 (13.0)	3 (13.6)	2 (12.5)	3 (9.7)	8 (13.3)
Rectal	4 (17.4)	1 (4.5)	0 (–)	7 (22.6)	7 (11.7)
Skin/soft tissue	1 (4.3)	1 (4.5)	1 (6.3)	3 (9.7)	5 (8.3)
Renal	2 (8.7)	2 (9.1)	2 (12.5)	1 (3.2)	4 (6.7)
Breast	2 (8.7)	1 (4.5)	1 (6.3)	1 (3.2)	3 (5.0)
Head and neck	1 (4.3)	1 (4.5)	0 (–)	3 (9.7)	3 (5.0)
Other[b]	3 (13.0)	4 (18.2)	4 (25.0)	3 (9.7)	8 (13.3)
WHO performance status					
0/1/2/missing	11/10/1/1	11/8/0/3	7/9/0/0	15/15/0/1	27/28/1/4

[a] Most frequent (≥5% of patients overall); [b] includes (n): right anterior thigh (1), melanoma on the right foot (1), left eye (1), chest wall (1), appendix (1), unknown primary (2) and chondrosarcoma of lung (1)

Table 2 Summary of pharmacokinetic parameters following single oral doses of cediranib 45 mg for fed and fasted states during Part A: pharmacokinetic analysis set

Pharmacokinetic parameter	Cediranib 45-mg fed state		Cediranib 45-mg fasted state		Point estimate of Gmean ratio of fed to fasted	94% CI of Gmean ratio of fed to fasted
	n	Gmean (CV%)	*n*	Gmean (CV%)		
AUC (ng h/mL)	30	1920 (62.03)	32	2392 (57.23)	0.762	0.663, 0.876
C_{max} (ng/mL)	31	87.3 (66.01)	33	127.9 (60.48)	0.672	0.567, 0.796

Food effect ratio = ratio of cediranib-fed Gmean: cediranib-fasted Gmean

Gmean geometric mean, *CV* coefficient of variation

the 45 mg fixed-dose and dose-escalation groups, respectively. In the fixed-dose group ($n = 16$), two patients were able to maintain their 45 mg/day dose longer than 6 weeks, while six patients required a dose reduction to 30 mg/day. In the dose-escalation group ($n = 31$), the MTD was 20 mg/day for two patients, 30 mg/day for 10 patients, 45 mg/day for five patients and 60 mg/day for two patients. The per protocol MTD was undefined for the remaining patients in the fixed-dose ($n = 8$) and dose-escalation ($n = 12$) groups due to insufficient drug exposure, i.e., <6 weeks continuous treatment.

Diarrhoea and hypertension were the most common adverse events in Part B (Table 3). There was a low overall incidence of CTC grade 3 adverse events, with the majority events occurring as single instances; seven patients experienced a grade 4 adverse event and four patients experienced a grade 5 adverse event. Overall, the incidence of adverse events was similar between the fixed- versus dose-escalation groups. Four cases (two fatal) of bowel perforation occurred during Part B; three in patients receiving 45 mg/day and one receiving 20 mg/day. Three of these patients were known to have disease directly involving the gastrointestinal tract or the abdominal cavity, and this was considered to be a confounding factor. The tumour types in these three patients were cancer of the appendix ('other'), ovarian cancer with gastrointestinal metastases and 'unknown' primary tumour with abdominal metastases.

ECG

Assessment of QTc in this study showed no clinically relevant changes following single or multiple dosing with cediranib 45 mg. The primary analysis in Part A compared baseline subtracted QTcF at the time of individual C_{max} with baseline subtracted QTcF at the corresponding time in the control arm. The day 8 data (post-1-week washout, predose) were used as a within-patient control. The mean effect was −3.343 ms (90% CI −9.13, 2.44; $P = 0.3329$), indicating no clinically relevant effect of cediranib on cardiac repolarisation as determined by QTcF. In Part B, the mean change from baseline in QTcF/QTcB was 0.3/−0.7 ms, −7.3/−8.5 ms and 2.4/−1.4 ms for the 45 mg fixed dose, and the 30 mg and 45 mg dose-escalation groups, respectively. Assessment of individual patient data did not suggest that multiple daily dosing with cediranib 45 mg causes any increase in QTcF or QTcB over time (note: no ECGs were taken during the short time interval when a small number of patients were receiving a dose higher than 45 mg).

Efficacy

In Part B, four patients experienced a best objective response of partial response (PR); one (7%) in the fixed-dose group and three (10%) in the dose-escalation groups. Stable disease (≥8 weeks) was reported for four (27%) and 9 (31%) patients in the fixed-dose and dose-escalation groups, respectively. PR primary tumour types consisted of ovarian cancer; head and neck; poorly differentiated (grade 3) tumour located in the peritoneum, and adenocarcinoma of unknown primary origin. In both the fixed-dose and dose-escalation groups, the majority of patients showed a reduction as their best response in tumour size, and there was no suggestion of a dose response (Fig. 2).

Pharmacodynamic results

Two initial scans were performed prior to Part A to define the reproducibility of the DCE-MRI parameters and volumes. The DCE-MRI parameters $IAUC_{60}$, K^{trans}, V_e, whole tumour volume and enhancing tumour volume were shown to have good reproducibility with CVs of approximately 10%; V_p was less reproducible with a CV of 38%. There was no difference between the DCE-MRI parameters from the two reproducibility scans performed prior to Part A and the baseline scan for Part B indicating that the two single doses of cediranib given during Part A, while known to cause an acute reduction in DCE-MRI parameters [3] did not have a sustained effect upon the tumour vascularity (data not shown).

DCE-MRI data from Part B showed an overall mean reduction from baseline for both median $IAUC_{60}$ and median K^{trans}, with a statistically significant mean decrease for K^{trans} at all visits (weeks 4, 8 and 16) and for $IAUC_{60}$

Table 3 Number of patients who had at least one adverse event in any category during Part B (with a total frequency of >15% in either the fixed-dose or the dose-escalation groups): safety analysis set

	Number of randomised patients[a]			
	Fixed dose		Dose-escalation[b]	
	Cediranib 45 mg $n = 16$		Cediranib 30–90 mg $n = 31$	
	All grades, *n* (%)	CTC grade ≥3, *n* (%)	All grades, *n* (%)	CTC grade ≥3, *n* (%)
Diarrhoea	13 (81)	1 (6)	25 (81)	4 (13)
Nausea	11 (69)	0 (–)	17 (55)	1 (3)
Hypertension	11 (69)	0 (–)	23 (74)	0 (–)
Vomiting	10 (63)	0 (–)	14 (45)	3 (10)
Constipation	10 (63)	0 (–)	11 (35)	0 (–)
Abdominal pain	5 (31)	1 (6)	10 (32)	5 (16)
Fatigue	5 (31)	2 (13)	10 (32)	1 (3)
Stomatitis	4 (25)	1 (6)	9 (29)	3 (10)
Decreased appetite	4 (25)	0 (–)	8 (26)	0 (–)
Dysphonia	4 (25)	0 (–)	7 (23)	0 (–)
Lethargy	4 (25)	0 (–)	7 (23)	0 (–)
Headache	5 (31)	0 (–)	5 (16)	0 (–)
Weight decreased	2 (13)	0 (–)	8 (26)	1 (3)
Anorexia	3 (19)	0 (–)	6 (19)	0 (–)
BTSH increased	2 (13)	0 (–)	7 (23)	0 (–)
Arthralgia	3 (19)	1 (6)	4 (13)	0 (–)
Back pain	1 (6)	0 (–)	6 (19)	1 (3)
Dizziness	1 (6)	0 (–)	6 (19)	0 (–)
Dyspepsia	3 (19)	0 (–)	3 (10)	0 (–)
Dry skin	3 (19)	0 (–)	1 (3)	0 (–)
Pharyngolaryngeal pain	3 (19)	0 (–)	0 (–)	0 (–)

CTC common terminology criteria version 3.0, *BTSH* blood thyroid-stimulating hormone

[a] Number of patients with adverse events, presented in decreasing order of frequency (all grades)

[b] The dose in the dose-escalation group represents the maximum dose attained prior to the adverse event

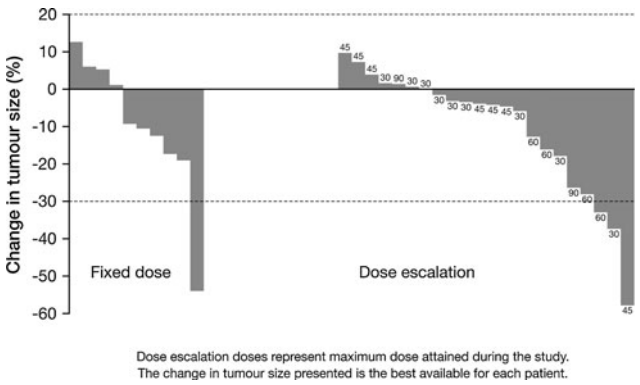

Fig. 2 Waterfall plot for best reduction in 1D tumour size (sun of the longest diameter) for each patient in either the fixed-dose group (cediranib 45 mg) or the dose-escalation group during Part B

at weeks 4 and 8 (Table 4). A parameter map for K^{trans} for a patient with a colorectal liver metastasis is shown in Fig. 3, demonstrating the reduction in K^{trans} observed after 16 weeks of cediranib therapy. It was noted that in two cases that patients with stable disease at week 16 did not achieve a reduction in $IAUC_{60}$ or K^{trans} until week 8. Statistically significant reductions in V_e (extracellular space volume fraction) and V_p appeared to occur later (at week 8) returning to previous levels by week 16. When considering these results, it should be noted that V_p is less reproducible as a parameter and that patient numbers at the later time points were limited to patients coming off study because of progressive disease. Although the reduction in whole tumour volume did not achieve statistical significance, an overall reduction in the enhancing tumour volume on MRI from baseline was observed at weeks 4, 8 and 16 (significant at week 4 and 16 $P \leq 0.05$) (Table 4).

The CT EnF was also analysed as an integrated measure of tumour vascularity and means of assessing the effects of cediranib. The data showed statistically significant

Table 4 Change (%) from baseline in MRI parameters over study period (up to and including week 16)

Parameter	Visit	*n*	% Change from baseline	95% CI	*P* value (2-sided)
$IAUC_{60}$	Week 4	6	−30.5	−50.5, −2.4	0.010
	Week 8	4	−33.2	−53.4, −4.4	0.009
	Week 16	4	−13.1	−39.3, 24.4	0.090
K^{trans}	Week 4	6	−36.2	−57.6, −4.0	0.009
	Week 8	4	−44.0	−65.3, −9.6	0.007
	Week 16	4	−32.6	−58.2, 8.7	0.002
V_e	Week 4	6	−13.8	−29.4, 5.2	0.029
	Week 8	4	−29.4	−44.9, −9.6	0.004
	Week 16	4	−12.9	−32.2, 11.8	0.053
V_p	Week 4	6	−29.5	−61.6, 29.4	0.050
	Week 8	4	−63.9	−82.7, −24.5	0.004
	Week 16	4	−23.0	−64.1, 65.5	0.105
Whole tumour volume	Week 4	6	−8.2	−29.0, 18.7	0.108
	Week 8	4	−11.1	−35.6, 22.6	0.098
	Week 16	4	−15.5	−39.7, 18.3	0.064
CT enhancing fraction	Week 8	5	−17.43	−68.8, 34.0	0.036
	Week 16	4	−25.14	−53.5, 3.2	0.028

Percentage change and CIs were determined from least squares estimates based on log-transformed data. Data were back-transformed prior to the calculation of percentage

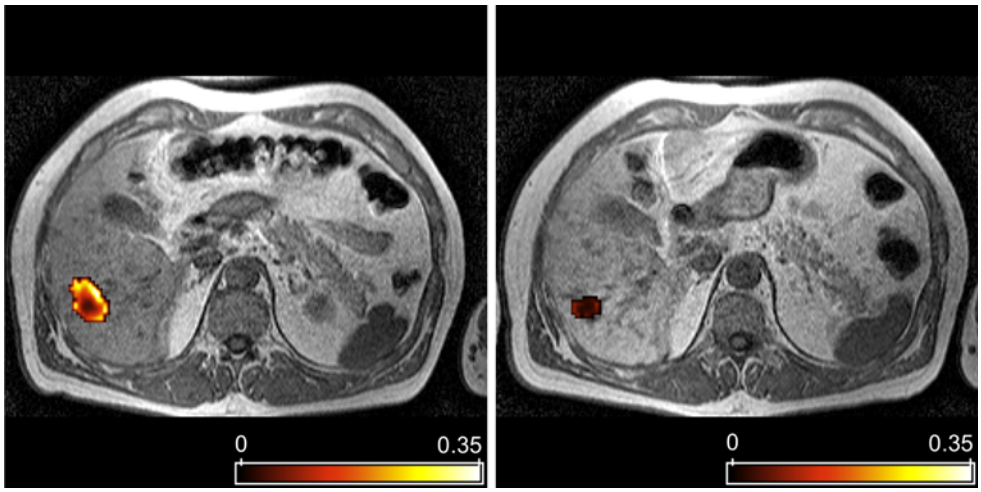

Fig. 3 Parameter map of K^{trans} of colorectal liver metastases at baseline and week 16 on continual therapy with cediranib. At baseline, a bright enhancing rim is visible corresponding with voxels with higher values of K^{trans}, this is diminished after 16 weeks of therapy

reductions in CT EnF at all four thresholds, which correlated with the DCE-MRI parameter findings. Of the patients that participated in DCE-MRI research, five patients with seven assessable tumours had lesions that were suitable for assessment using CT EnF analysis. One patient who participated in the DCE-MRI study for Part B was excluded from analysis due to CT contrast agent allergy. Analysis of the CT data showed that the whole tumour volume defined on standard CT correlated strongly to the equivalent whole tumour volume defined on DCE-MRI (Spearman's correlation $\rho = 0.955$). All four thresholds showed reductions in enhancement with an average reduction in enhancing fraction at week 8 of −17.43% and week 16 −25.41% ($P = 0.036$ and $P = 0.028$, respectively). This is consistent with a sustained antivascular effect of cediranib. The results from the separate visits were pooled to explore the relationship between the CT EnF and DCE-MRI parameters. CT EnF was not observed to correlate with either MRI enhancing tumour volume or enhancing fraction. The CT EnF at each threshold correlated significantly with the MRI modelled parameters of $IAUC_{60}$ (Spearman's correlation $\rho = 0.890$, 0.863, 0.812 and 0.678 for 50, 60, 70 and 80 HU, respectively, $P \leq 0.005$) and K^{trans} (Spearman's correlation $\rho = 0.881$, 0.869, 0.853, 0.782 for 50, 60, 70 and 80 HU, respectively, $P \leq 0.005$), implying that CT EnF may have potential as an alternative measure of tumour vascularity in the assessment of cediranib and other antiangiogenic agents.

Discussion

This two-part Phase II study was designed to determine the effect of food on the pharmacokinetics of cediranib (Part A) and to assess the tolerability and efficacy of multiple doses of cediranib in patients with advanced solid tumours (Part B). In Part A, the pharmacokinetic assessment showed a modest reduction in AUC and C_{max} in the presence of food, and it is therefore recommended that cediranib be administered at least 1 h before or 2 h after food. A food effect on pharmacokinetics is not unique to cediranib amongst anti-angiogenic agents. The pharmacokinetics of axitinib and sorafenib are also affected by food [22] (NEXAVAR Prescribing information 2009). As with cediranib, the recommendation is that sorafenib be administered at least 1 h before or 2 h after food.

Patients generally tolerated cediranib well at the average dose, with some patients tolerating higher doses with the dose-escalation arm. The tolerability profile of cediranib in this study was consistent with previous studies—diarrhoea, nausea and hypertension were the most common adverse events, and these were manageable [3, 4, 23–25]. There were no important differences in the safety and tolerability of cediranib when given as either a fixed-dose or using a dose-escalation approach. In both groups, the average daily dose was approximately 30 mg/day. Only a minority of patients were able to tolerate cediranib $\geq$45 mg for $\geq$6 weeks and for most patients a 30 mg dose appears to be more sustainable for chronic dosing. Importantly, no clinically relevant effect of cediranib on cardiac repolarisation, as determined by QTcF and QTcB, was detected following single oral dose of cediranib 45 mg (Part A) or following multiple daily dosing (Part B). A preliminary assessment of activity provided encouraging results in a broad range of tumours, consistent with results of an earlier Phase I study of cediranib [3]. The efficacy data provide encouraging evidence antitumour activity in both the fixed-dose and dose-escalation groups, with no evidence of a dose response.

An exploratory objective in Part B was to assess the effects of cediranib on tumour blood flow and permeability using DCE-MRI. Our results have shown for the first time that cediranib has a sustained effect upon extracranial tumour vasculature up to 16 weeks after starting continuous cediranib therapy in patients. These effects were detected by DCE-MRI scanning and by applying CT enhancement techniques. The effects of cediranib on DCE-MRI parameters on extracranial tumour vasculature have previously been established within the Phase I setting [3]. This earlier study assessed the treatment effect upon liver metastases up to a maximum of 56 days therapy; the acute vascular effects of cediranib were observed in DCE-MRI assessments following 2 days of therapy. In this study, only $IAUC_{60}$ and K^{trans} were reported, with $IAUC_{60}$ being the primary outcome measure. Our current study applied the 'extended Tofts' model of tracer kinetics allowing the parameters of $IAUC_{60}$, K^{trans}, V_p and V_e to be determined with the period of follow-up on DCE-MRI extending to week 16. The purpose of the trial was to evaluate the effects of chronic dosing of cediranib on tumour vasculature; the earliest assessment within the study was after 4 weeks of continual therapy. At this time point, significant reductions were observed in the average parameters; however, in some individual patients with stable disease up to at least 16 weeks, the development of reductions in $IAUC_{60}$, K^{trans} and V_p did not occur until later at week 8.

These late decreases in the DCE-MRI parameters may potentially represent the effects of VEGF signalling inhibition on blood volume and vessel size similar to those observed in previous studies [2]. Reduction in blood vessel volume and hence V_p in turn could lead to a reduction in the parameter of K^{trans} (the transfer constant co-efficient) due to the impact upon tumour blood flow, as K^{trans} is a composite parameter reflecting both blood flow and capillary permeability. The data potentially could be interpreted to suggest that the early reductions in K^{trans} may relate to the reduction in capillary permeability induced by the drug, whereas the later and persistent decreases in the parameters may reflect vascular normalisation in line with the later reduction in V_p. However, the parameter V_p is only significantly reduced at week 8, and this is not sustained to week 16, which may relate to the small numbers of patients remaining on the study at the later time point. Ideally, studies with a larger number of participants are required in order to test this hypothesis. The development of late-onset statistically significant imaging effects has not been reported before and implies that early clinical and biomarker evaluation of anti-angiogenic agents should be extended to approximately 8 weeks before concluding that an agent is biologically inert.

The use of CT-calculated EnF applied to standard contrast-enhanced anatomical CT scans, which were originally requested for RECIST analysis before entry to the trial, has not been used previously to evaluate the effects of VEGF inhibition on tumour vascularity. The data demonstrate a reduction in the CT EnF following commencement of continual cediranib therapy up to week 16, with CT EnF values correlating to the DCE-MRI parameters $IAUC_{60}$ and K^{trans}. The difference in correlations of CT EnF at the different Hounsfield unit thresholds may relate to the difference in specificity of thresholds to tumour vascularity, with the 50HU threshold being the least specific for vascular areas and more likely to incorporate both vascular and non-vascular areas. DCE-MRI parameters represent different compartments and properties of the tumour; therefore, the relationship between the DCE-MRI parameters and CT EnF at each threshold will vary. Although the CT EnF is

less physiologically specific than DCE-MRI parameters, it is an attractive method of vascular assessment, as it can be performed as a supplementary analysis on routine scans eliminating the need for additional visits or further radiation exposure.

In conclusion, this study showed that food has a modest effect on the pharmacokinetics of cediranib, and it is recommended that cediranib be administered at least 1 h before or 2 h after food. Cediranib was generally well tolerated with a manageable safety profile and encouraging antitumour activity was observed in this patient population with advanced disease. The 30-mg dose appeared to be most sustainable for chronic dosing. Cediranib did not cause QTc prolongation. Continuous once-daily dosing with cediranib had extended effects upon tumour vascularity up to week 16 as measured by reductions in DCE-MRI parameters, with some patients showing first significant reductions as late as week 8. The retrospective CT enhancing fraction analysis illustrates the potential role this technique may have in the assessment of antiangiogenic agents.

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Conflict of interest None.

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