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Cediranib in combination with various anticancer regimens: results of a phase I multi-cohort study

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Summary

Background—Cediranib is a highly potent vascular endothelial growth factor (VEGF) signaling inhibitor of all three VEGF receptors. This phase I, single-center, dose-finding study was designed primarily to investigate the safety and pharmacokinetics (PK) of cediranib with various anticancer regimens in patients with advanced solid tumors.

Experimental design—Oral cediranib 20, 30, and/or 45 mg/day was given in combination with standard mFOLFOX6; docetaxel; irinotecan; irinotecan and cetuximab; or pemetrexed. The novel study design allowed simultaneous evaluation of the safety and PK of these regimens with cediranib in one study. Secondary assessments included a preliminary evaluation of efficacy.

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Results—Fifty-nine patients received cediranib and were evaluable for safety. The most common adverse events across the study were fatigue and diarrhea (both *n*=52). The most common CTC grade≥3 adverse events were neutropenia (*n*=19) and fatigue (*n*=16). Cediranib did not appear to have a major effect on the PK profile of any chemotherapy agent tested. A preliminary assessment of efficacy showed that objective responses were achieved in some patients (*n*=6) who had previously progressed on similar regimens without cediranib.

Conclusion—In this group of heavily pretreated patients, the study design permitted simultaneous assessment of multiple treatment arms. Treatment with cediranib and the various anticancer regimens was generally well tolerated, with no apparent PK interaction and preliminary evidence of antitumor activity.

Keywords

Antiangiogenic agent; Cediranib; Clinical trial; phase I; Combination drug therapy; Multi-cohort study

Introduction

Cediranib (RECENTIN™) is an oral and highly potent vascular endothelial growth factor receptor (VEGFR) signaling inhibitor with activity versus all three VEGFRs (VEGFR-1, -2, and -3) [1]. Recent trials have shown that combining an agent that targets vascular endothelial growth factor (VEGF) signaling with certain chemotherapies provides clinical benefit in patients with breast cancer [2], colorectal cancer (CRC) [3, 4], and non-small-cell lung cancer (NSCLC) [5]. The present study investigated cediranib in combination with selected chemotherapy regimens in patients with advanced solid tumors. Preclinical investigations have shown broad-spectrum antitumor activity of cediranib in a range of histologically diverse xenograft models [1, 6]. Early clinical evaluation in patients with a broad range of advanced solid tumors has demonstrated that cediranib monotherapy was generally well tolerated at doses≤45 mg/day and has a pharmacokinetic profile that supports once-daily oral administration [7]. The most frequently reported adverse events were fatigue, nausea, diarrhea, and hypertension [7].

Several phase I combination studies have shown that cediranib can be combined with standard doses of cytotoxic chemotherapy. Cediranib 30 mg in combination with standard doses of carboplatin/paclitaxel and gemcitabine/cisplatin was shown to be active and tolerable in patients with advanced NSCLC [8, 9]. More recently, cediranib 30 mg in combination with mFOLFOX6 was also demonstrated to be active and tolerable in patients with advanced CRC and was recommended for further investigation [10]. The available data did not suggest any potential for a major pharmacokinetic interaction if cediranib was dosed in combination with any of the chemotherapy regimens selected for investigation in the present study.

The primary objective of this phase I, single-center, dose-finding study (ClinicalTrials.gov Identifier: NCT00502567; AstraZeneca study code 2171IL0008) was to establish the safety and tolerability of cediranib when given in combination with mFOLFOX6, docetaxel, irinotecan, irinotecan and cetuximab, or pemetrexed to patients with previously treated,

advanced solid tumors who could potentially benefit from the combination treatment. Based on a single Institutional Review Board procedure, the study design allowed for the simultaneous assessment of cediranib in combination with five standard anticancer regimens used in current clinical practice. This parallel approach to conducting phase I studies under a single protocol has been described previously [11].

Materials and methods

Patients

Adult patients (≥18 years) with advanced solid tumors refractory to standard treatment were recruited in a single center. All patients had histologically confirmed metastatic cancer, not amenable to surgery or radiation therapy with curative intent, and had a measurable lesion by computed tomography or other techniques according to Response Evaluation Criteria In Solid Tumors (RECIST version 1.0) [12]. Patients were required to have a WHO performance status of 0-2 and a life expectancy of at least 12 weeks. The main exclusion criteria were brain metastases or spinal cord compression, unless irradiated at least 4 weeks before study entry and stable without steroid treatment for ≥1 week; massive pleural effusions or ascites unless drained; no chemotherapy within the 4 weeks prior to the start of study; inadequate bone marrow reserve; history of poorly controlled hypertension (resting blood pressure consistently >150/100 mm Hg with or without a stable dose of antihypertensive medication); active gastrointestinal disease affecting the absorption of cediranib; surgery within 2 weeks prior to the study (excluding placement of vascular access) or incompletely healed surgical incision. Patients were required not to take any medication that could markedly affect renal function or significantly modulate hepatic drug metabolizing activity by way of enzyme induction or inhibition. The trial was approved by the relevant Institutional Review Board, and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca policy on bioethics. Each patient provided written informed consent.

Study design

In a single protocol, three once-daily oral doses of cediranib (20, 30, and/or 45 mg) were evaluated in combination with five separate anticancer regimens. (Fig. 1a). Cediranib was administered in combination with: (arm 1) mFOLFOX6 given as standard 14-day cycles (oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2, each given intravenously over 2 hours; followed by 5-FU 400 mg/m^2 bolus given over 2-4 minutes and then 5-FU 2400 mg/m^2 given intravenously over 46 hours); (arm 2) docetaxel 75 mg/m^2 given intravenously over 60 min every 21 days, (arm 3A) irinotecan 300 mg/m^2 given intravenously over 90 min repeated every 21 days; (arm 3B) irinotecan given with cetuximab (given as a 20 mg test dose on day 1, followed by a 400 mg/m^2 initial loading dose administered as an 120-minute infusion; the recommended weekly maintenance dose thereafter was 250 mg/m^2 infusion given over 60 min), and (arm 4) pemetrexed 500 mg/m^2 given intravenously over 10 min repeated every 21 days.

Patient enrollment was concurrent across all treatment arms with the exception of arm 3B (cediranib+irinotecan+cetuximab), which could be explored once three patients in arm 3A

(cediranib 30 mg in combination with irinotecan) had completed two 21-day cycles of treatment with no dose-limiting toxicities (DLTs). Dose modifications and delays in treatment for each of the cytotoxic regimens were performed according to previously published guidelines for these regimens and the package inserts [13–17].

The starting dose of cediranib was 30 mg in arms 1, 2, 3A and 4, and 20 mg in arm 3B. In all arms, treatment with cediranib commenced 2 days after the first administration of chemotherapy (day 3). Initially, three patients in each of arms 1, 2, 3A, and 4 received cediranib 30 mg in combination with chemotherapy. In arm 3B, six patients were planned to be recruited directly into the cediranib 20 mg cohort. In order to be evaluable for dose-escalation decisions, patients were required to complete at least two cycles of chemotherapy while receiving at least 75% of the planned daily dose of cediranib, or they experienced a DLT. Dose-escalation decisions were made according to the number of DLTs, which occurred in each cohort according to Fig. 1b. The maximum tolerated dose (MTD) for each arm was determined based on DLTs occurring during the first two cycles of each treatment arm. If a DLT was observed in 2/6 patients within a dose cohort, that dose was considered to exceed the MTD and dose escalation was stopped.

An adverse event was considered as a DLT if it met one of the criteria below and it occurred within the first two cycles of treatment and it was considered to be related to the combination of chemotherapy and cediranib. A DLT was defined as grade 3 or higher hypertension; or any other grade 3 or higher non-hematological adverse event or a CTC grade 4 hematological adverse event, which lasted 5 or more days. Adverse events were recorded throughout the study and graded according to the National Cancer Institute Common Terminology Criteria (CTC), version 3.0.

Blood pressure, heart rate, ECG, hematology, clinical chemistry, and urinalysis (including pH, blood, protein, glucose, ketones, and bilirubin) were measured at scheduled assessments throughout the treatment period.

Pharmacokinetic assessments

Pharmacokinetic sampling schedules were devised to obtain robust pharmacokinetic information while taking into consideration the need to conduct this study on an outpatient basis. Serial blood samples were obtained on day 1, cycle 1 to determine the pharmacokinetic profiles of 5-FU, oxaliplatin (quantified as total platinum), docetaxel, pemetrexed, irinotecan, and SN38 (active metabolite of irinotecan) when given alone. In addition, serial blood samples were obtained on day 1, cycle 2 to determine the pharmacokinetic profile of the agents listed above in the presence of cediranib when dosed to steady state. Serial blood samples obtained on day 1, cycle 2 were also used to determine the steady-state pharmacokinetic parameters of cediranib when given with the chemotherapy agents listed above. Full details of sample schedules are described below.

In arm 1, blood samples for 5-FU were obtained 1 h into the infusion on day 1 and at the end of the 46 hour-infusion (cycles 1 and 2). Blood samples for oxaliplatin were obtained predose, at the end of the 120-minute infusion, and at 0.25, 05, 0.75, 1, 3, 5, 22, 24, and 46 h post-infusion (cycles 1 and 2). In arm 2, blood samples for docetaxel were obtained

preinfusion, 30 min after the start of infusion, at the end of the 60-minute infusion, and at 0.5, 1, 2, 3, 5, 23, 25, and 47 h post-infusion on day 1 (cycles 1 and 2). In arm 3, blood samples for irinotecan were obtained preinfusion, 45 min after the beginning of infusion, at the end of the 90-minute infusion, and at 5, 10, 15, 30 min and 1, 2, 4, 6, 22, 24, and 46 h post-infusion on day 1 (cycles 1 and 2). In arm 4, blood samples for pemetrexed were obtained preinfusion, at end of the 10-minute infusion, and at 5, 10, 30, 45 min and 1, 2, 4, 6, 8, and 24 h post-infusion on day 1 (cycles 1 and 2). In all arms, blood samples for cediranib were obtained predose on day 8 (cycle 1), predose, and 1, 2, 4, 6, 8, and 24 h post-dose on day 1 (cycle 2), and predose on days 8 and 15 (cycle 2). Cediranib was given to patients in an upright position with 240 mL of water as a once-daily oral tablet at approximately the same time each morning, not less than 1 h before or 2 h after eating. All blood samples were analyzed using validated analytical methods. Pharmacokinetic parameters were calculated using standard non-compartmental analysis [7].

Tumor response evaluation

Baseline tumor assessments were performed no more than 4 weeks before planned first dosing with cediranib. Follow-up assessments were performed at the end of every two cycles of chemotherapy treatment (ie every 28 days in arm 1 and every 42 days in arms 2, 3, and 4). Response was classified according to RECIST.

Statistical analyses

Most data analyses were descriptive with no comparative statistical analysis. For the pharmacokinetic parameters of area under the plasma concentration–time curve (AUC) and maximum plasma concentration (C_{max}), $\log_e$-transformed data were analyzed by analysis of variance (ANOVA), fitting patient and regimen (chemotherapy alone or chemotherapy +cediranib) as factors. In each arm, point estimates and corresponding 90% confidence intervals (CIs) were provided for the difference between the chemotherapy of interest ±cediranib. The point and interval estimates from the fitted model were then exponentially back-transformed to provide a point estimate and corresponding 90% CI for the ratio of cediranib+chemotherapy versus chemotherapy. The possibility that the effect of any interaction is affected by the dose of cediranib was assessed visually, using appropriate graphical displays. Assumptions underlying the fitted model were assessed by inspection of residual plots. Homogeneity of variance was assessed by plotting the studentized residuals against the predicted values from the model, whilst normality was assessed by use of normal probability plots. If these assumptions were believed to be violated, alternative data transformations or other statistical techniques were employed.

Results

Patients

Sixty patients were enrolled between January 2005 and March 2006 (Table 1); among these, 59 received at least one dose of study medication and were evaluable for safety. Most of the patients in this study were heavily pretreated with prior chemotherapy regimens for advanced disease; only two patients (one each in the mFOLFOX6 and docetaxel arms) had

not received prior chemotherapy. The majority of patients in each arm (65% total) had received 3 or more previous chemotherapy regimens.

Safety and tolerability

The two most common adverse events across the study were fatigue and diarrhea (Table 2); two patients discontinued due to fatigue and three due to diarrhea. Other commonly occurring adverse events are also shown in Table 2. The most common adverse events in each arm were: arm 1, fatigue (*n*=12 [86%]), diarrhea (*n*=11 [79%]) and neutropenia (*n*=10 [71%]); arm 2, diarrhea (*n*=11 [92%]), fatigue (*n*=10 [83%]) and anorexia (*n*=8 [67%]); arm 3A, diarrhea (*n*=15 [94%]), fatigue (*n*=15 [94%]), and vomiting (*n*=12 [75%]); arm 3B, diarrhea, fatigue, and nausea (all *n*=5 [100%]); arm 4, diarrhea (*n*=10 [83%]), fatigue (*n*=10 [83%]), and hypertension (*n*=9 [75%]). Across all arms, the most common CTC grade 3 or 4 adverse events of any causality were neutropenia (19 patients [32%]; grade 3, 11 patients; grade 4, 8 patients), fatigue (16 patients [27%]), leukopenia (13 patients [22%]; grade 3, nine patients; grade 4, four patients), and diarrhea (12 patients [20%]). Neutropenia, fatigue, and leukopenia were the most commonly reported serious adverse events occurring in 18 (30%), 16 (27%), and 12 (20%) patients, respectively.

Most hypertension adverse events were CTC grade 1 (21 patients [35%]); six patients (10%) experienced CTC grade 2 and three patients (5%) experienced CTC grade 3 hypertension. Three patients had serious adverse events of hypertension. Hypertension was managed successfully with antihypertensive medication and none of the hypertensive events led to discontinuation of study treatment or met the criteria for a DLT.

The DLTs for each study arm are summarized in Fig. 2. The MTD of cediranib was 30 mg when given in combination with docetaxel (arm 2) or pemetrexed (arm 4). However, for arm 2 this conclusion should be interpreted with caution as three patients in the cediranib 30 mg cohort did not meet the 75% dose intensity criterion for evaluability as defined in the protocol. When given in combination with mFOLFOX6 or irinotecan the MTD of cediranib was 20 mg. Although the combination of cediranib with irinotecan and cetuximab 20 mg was tolerated during the first two cycles, all five patients who received this combination developed CTC grade 3 diarrhea in later cycles.

Increases in blood thyroid-stimulating hormone (TSH) above the normal range (> 5 mU/L) were observed in 26 patients overall, but in the majority of cases free T4 and T3 remained within normal limits. There were two reported adverse events of CTC grade 1 hypothyroidism. Seven patients experienced adverse events of proteinuria (all CTC grade 1 or 2), across all study arms with the exception of arm 4. Fourteen patients (24%) reported neutrophil counts of less than 1×10^9/L and 27 patients (46%) had platelet counts below the normal range on at least one occasion, however there were no discontinuations from study treatment as a result of neutropenia, febrile neutropenia, or thrombocytopenia. There were no clinically relevant trends related to liver or kidney function, ECG, physical findings, or other safety observations.

Pharmacokinetics

The steady-state pharmacokinetics parameters of cediranib 30 mg in this study are comparable with those seen previously with cediranib given as a single agent following multiple once-daily oral doses of 30 mg (Table 3). Based on limited pharmacokinetic data, cediranib did not appear to have a major effect on the pharmacokinetic profile of any chemotherapy agent tested (oxaliplatin, 5-FU, pemetrexed, irinotecan [SN38], and docetaxel), ie there was a <2-fold change in the geometric mean chemotherapy pharmacokinetic parameters when given alone or in combination with cediranib (Table 3, Supplementary Fig. 3).

Efficacy

Efficacy data were available for 46 patients, 35 of whom were evaluable according to RECIST. There were four partial tumor responses: prostate cancer (arm 2, *n*=1); rectal cancer (arm 3A, *n*=1); CRC (arm 3B, *n*=1); lung cancer (arm 4, *n*=1) (Table 4). The median duration of treatment for these four patients was 319 days (range 154-384). A further 26 patients experienced stable disease comprising lung cancer (*n*=9), CRC (*n*=6), prostate and rectal cancer (both *n*=2), and tumors of the abdomen, breast, occipital, pleura, skin/soft tissue, renal pelvis and ureter, and unknown (all *n*=1). Some of the partial responses and stable diseases were reported in patients who had previously demonstrated resistance to similar regimens without cediranib. Three patients who were previously treated and subsequently failed with a docetaxel-containing regimen achieved either partial response or stable disease when cediranib was added to docetaxel. One patient who was previously treated and subsequently failed with a pemetrexed-containing regimen also achieved stable disease when cediranib was added to pemetrexed. One patient who was previously treated and subsequently failed with a bevacizumab-containing regimen achieved stable disease with cediranib and pemetrexed. One patient who was previously treated and subsequently failed with a cetuximab-containing regimen achieved stable disease with cediranib, irinotecan, and cetuximab.

Discussion

The multi-arm design of this phase I study permitted the simultaneous assessment of cediranib with five anticancer regimens. By being conducted in a single institution, the study gave the investigators valuable experience in using cediranib in combination with multiple regimens.

Cediranib in combination with selected chemotherapy regimens has been generally well tolerated with manageable toxicities, with a total of 12 (20%) patients discontinuing due to adverse events. The adverse-event profile is similar to that seen with cediranib monotherapy [7] and combination [8] studies with the expected addition of myelosuppression as a result of the chemotherapy. Fatigue and diarrhea were the most common adverse events across the entire study; these were also the most common CTC grade 3 cediranib-related adverse events. Two patients discontinued due to fatigue and three due to diarrhea. Fatigue and diarrhea are both commonly occurring adverse events reported in other cediranib studies and are also associated with the chemotherapy regimens used in this study. These adverse events

were manageable with dose interruptions and/or dose reductions along with continued supportive care.

Hypertension is likely to be a class effect of VEGF signaling inhibitors, as it has been observed with other agents that target VEGF [18–24]. Both preclinical [25] and clinical data [7] have revealed that hypertension is a common effect of cediranib treatment. In our trial, hypertension was managed by early intervention with anti-hypertensive agents and calcium-channel blockers were the preferred initial approach. Thirty patients (50%) experienced an adverse event of hypertension, but most were CTC grade 1 (21 patients [35%]). Hypertension was observed as a serious adverse event in three patients. However, none of the reports of hypertension led to discontinuation of study treatment and none met the criteria for a DLT. In the majority of cases hypertension occurred early in treatment (within the first 4 weeks of treatment), which is similar to the findings of a phase I study of pazopanib, an inhibitor of VEGFR and platelet-derived growth factor receptor [26].

In this study population of heavily pretreated patients with advanced cancer, the combinations of cediranib 20 mg with standard mFOLFOX6 or irinotecan, and cediranib 30 mg with docetaxel or pemetrexed were considered sufficiently well tolerated to undergo further evaluation in other clinical trials. Although the combination of cediranib 20 mg with irinotecan and cetuximab was tolerated during the first two cycles and was defined as the MTD according to the protocol definition, all five patients who received this combination developed CTC grade 3 diarrhea in later cycles.

A previous phase I study had concluded that cediranib 30 mg/day was the recommended phase II dose in combination with mFOLFOX6 [10]. In that study cediranib 20 mg/day was not investigated as no DLTs were observed at the 30 mg/day dose level, although the investigators did state that the majority of patients required a dose modification of cediranib and/or mFOLFOX6. They also reviewed the available data at the time and concluded that cediranib 30 mg or lower is likely to be tolerated in combination with other antitumor agents. In this context, it is worth noting that the 20 mg dose was taken forward into phase III investigation in combination with FOLFOX or XELOX (capecitabine with oxaliplatin) [27].

The steady-state pharmacokinetic parameters of cediranib in combination with oxaliplatin, 5-FU, pemetrexed, irinotecan [SN38], and docetaxel are comparable with those seen previously with cediranib monotherapy at the same dose level. In this study, cediranib did not appear to have a major effect on the pharmacokinetic profile of oxaliplatin, 5-FU, pemetrexed, irinotecan [SN38], and docetaxel (ie no pharmacokinetic interactions were observed that appear to necessitate dose modifications of the standard chemotherapy agents when given in combination with cediranib). Taken together with the safety data, these pharmacokinetic results suggest that cediranib with these selected anticancer agents at standard doses should undergo further clinical evaluation.

This study was designed primarily to investigate the safety and pharmacokinetic profile of cediranib in combination with selected chemotherapy regimens. There was preliminary evidence of antitumor activity in this broad population of heavily pretreated patients, even in

those who had previously received and failed the same chemotherapy regimen without cediranib.

In conclusion, once-daily oral administration of cediranib 30 mg in combination with docetaxel or pemetrexed, or 20 mg in combination with mFOLFOX6 or irinotecan was generally well tolerated in patients with advanced solid tumors. Cediranib is currently in phase III development in patients with CRC (in combination with FOLFOX) [27] and recurrent glioblastoma and the potential utility of cediranib (as a single agent and in combination) also continues to be investigated in a range of other tumors including lung cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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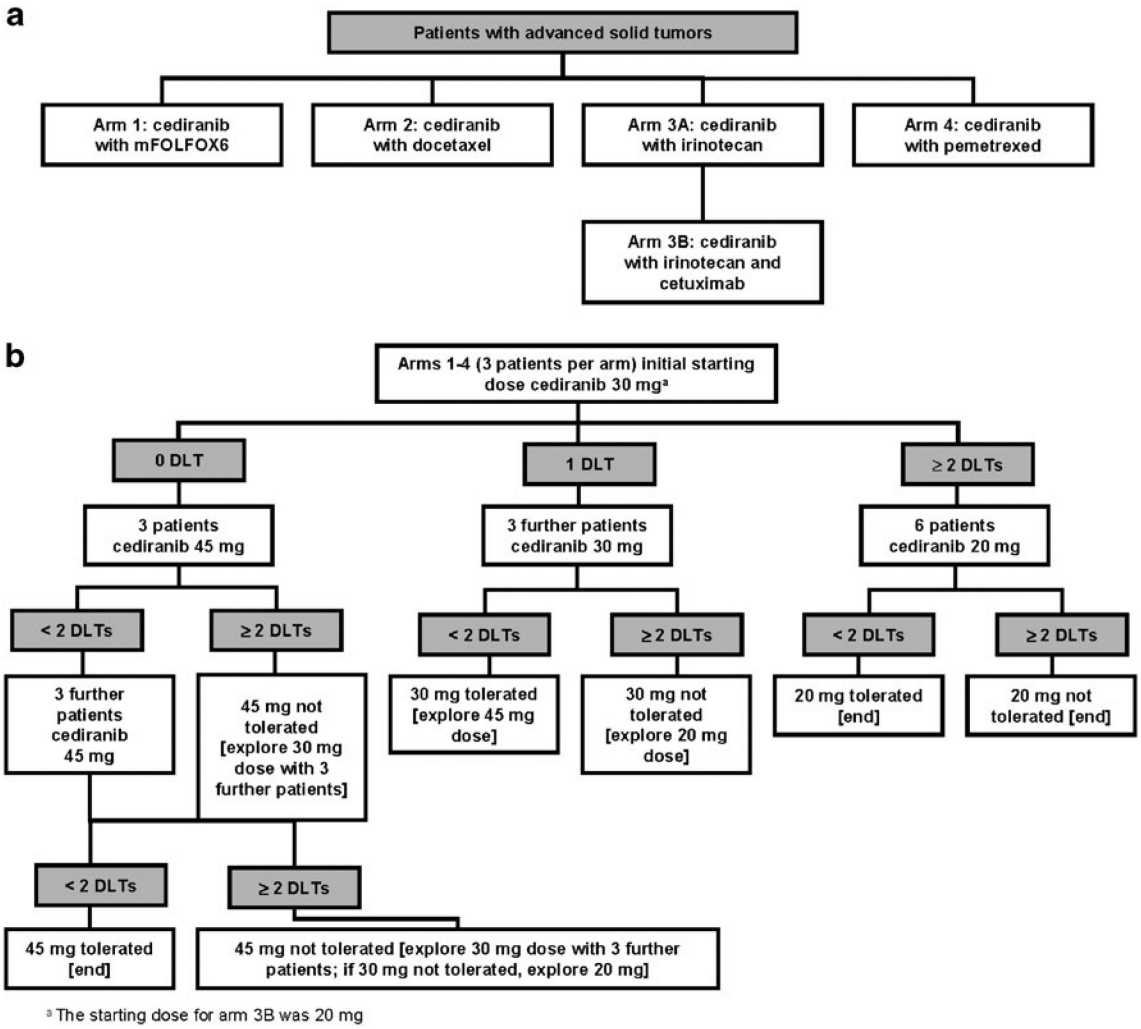
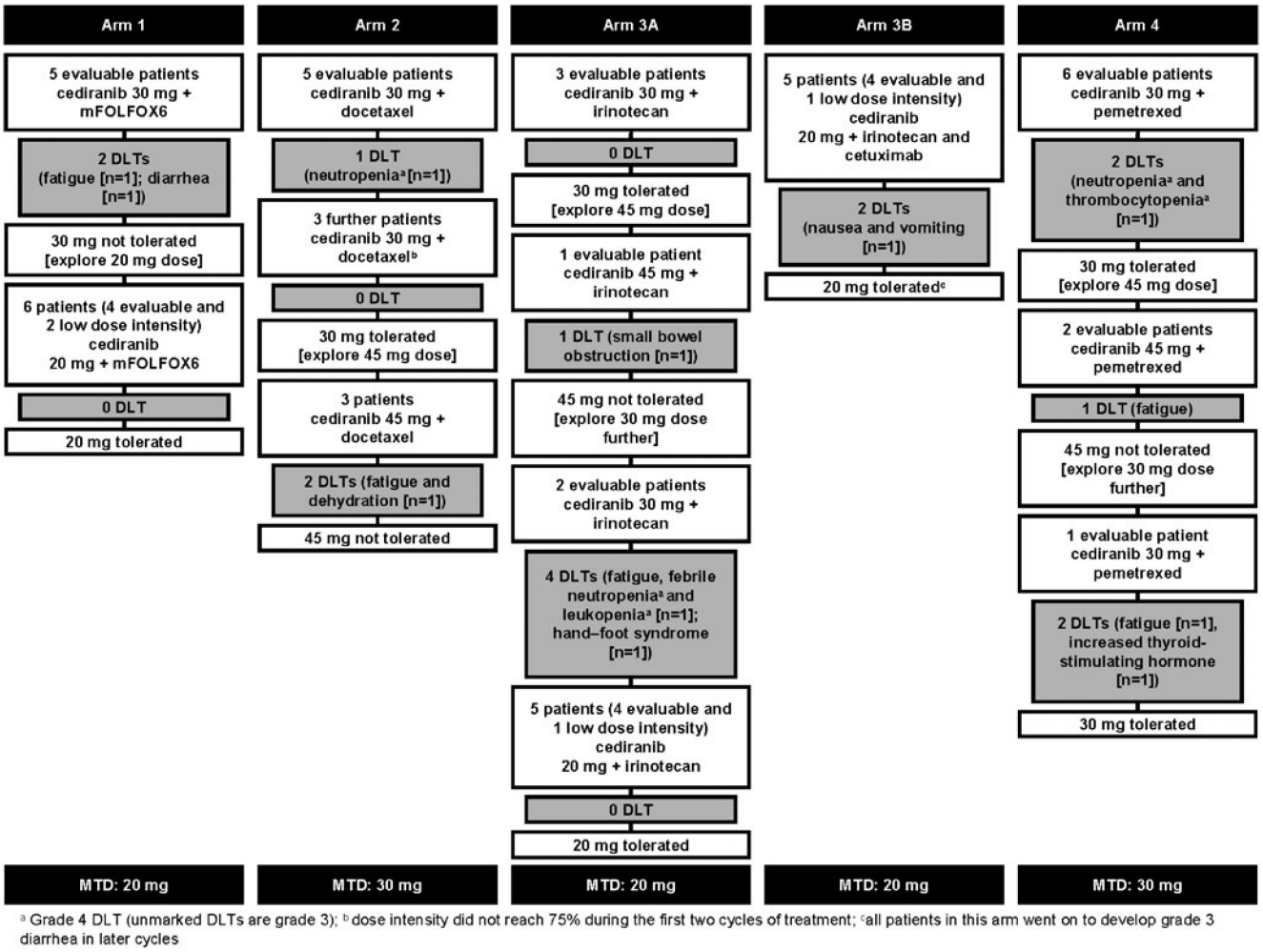


Fig. 1.

Study design. **a** Treatment arms, and **b** determination of maximum tolerated dose



[a] Grade 4 DLT (unmarked DLTs are grade 3); [b] dose intensity did not reach 75% during the first two cycles of treatment; [c] all patients in this arm went on to develop grade 3 diarrhea in later cycles

Fig. 2.
Dose-limiting toxicities

Table 1

Patient characteristics

	Arm 1 (*n* =14)	Arm 2 (*n* = 12)	Arm 3A (*n* =16)	Arm 3B (*n* =5)	Arm 4[a] (*n* =13)
Age (years)					
Mean (SD)	57 (12)	63 (9)	52 (13)	49 (8)	55 (14)
Range	35-80	44-75	31-71	39-59	27-74
Age group (years)					
> 18-65	12	8	13	5	10
>65	2	4	3	-	3
Race					
Caucasian	11	12	15	5	10
Black	3	-	1	-	2
Asian	-	-	-	-	1
Sex					
Male	5	9	10	1	5
Female	9	3	6	4	8
Baseline WHO performance status					
0	3	2	2	2	3
1	9	10	13	3	9
2	2	-	-	-	1
Unknown	-	-	1	-	-
Primary tumor type					
Lung	-	1	7	1	8
Colorectal	9	1	-	3	-
Pancreas	-	-	3	-	1
Breast	1	-	2	-	-
Renal cell	1	1	-	-	-
Prostate	-	2	-	-	-
Other[b]	3	7	4	1	4
Relevant surgery	14	12	14	5	12
Previous immunotherapy/hormonal therapy	1	3	1	0	0
Previous radiotherapy	6	7	11	2	9
Previous chemotherapy	13	11	16	5	13
1 regimen	2	1	3	0	2
2 regimens	2	3	1	2	1
3 regimens	1	2	8	0	5
>3 regimens	8	5	4	3	5

Arm 1: cediranib+mFOLFOX6; arm 2: cediranib+docetaxel; arm 3A: cediranib+irinotecan; arm 3B: cediranib + irinotecan and cetuximab; arm 4: cediranib+pemetrexed

[a] Includes one patient who did not receive study treatment and was excluded from the safety analysis

[b] Other tumor types included: abdomen, biliary tract, bladder, bone, esophagus, neurofibrosarcoma, occipital, ovary, peritoneum, pleura, prostate, rectal, renal/pelvis/ureter, skin/soft tissue, thyroid, unknown

Table 2

Safety and tolerability. Incidence of commonly occurring adverse events occurring at any time during the study (reported in≥25% of patients overall)

	Arm 1 (*n*= 14)		Arm 2 (*n*= 12)		Arm 3A (*n*=16)		Arm 3B (*n*=5)		Arm 4 (*n*= 12)		Total (*n*=59)
	Any grade (%)	Grade 3/4	Any grade (%)	Grade 3/4	Any grade (%)	Grade 3/4	Any grade (%)	Grade 3/4	Any grade (%)	Grade 3/4	Any grade (%)
Diarrhea	11 (79%)	3/0	11 (92%)	-	15 (94%)	3/0	5 (100%)	5/0	10 (83%)	1/0	52 (88%)
Fatigue	12 (86%)	3/0	10 (83%)	3/0	15 (94%)	6/0	5 (100%)	2/0	10 (83%)	2/0	52 (88%)
Nausea	8 (57%)	1/0	4 (33%)	-	11 (69%)	1/0	5 (100%)	1/0	8 (67%)	-	36 (61%)
Hypertension	9 (64%)	-	6 (50%)	2/0	5 (31%)	-	1 (20%)	-	9 (75%)	1/0	30 (51%)
Vomiting	5 (36%)	1/0	3 (25%)	-	12 (75%)	2/0	4 (80%)	1/0	6 (50%)	-	30 (51%)
Neutropenia	10 (71%)	6/0	5 (42%)	1/3	8 (50%)	2/3	1 (20%)	1/0	3 (25%)	1/2	27 (46%)
Anorexia	7 (50%)	-	8 (67%)	-	5 (31%)	-	2 (40%)	-	3 (25%)	-	25 (42%)
Decreased weight	5 (36%)	-	3 (25%)	-	6 (38%)	-	3 (60%)	-	4 (33%)	-	21 (36%)
Leukopenia	6 (43%)	2/0	4 (33%)	3/1	6 (38%)	1/3	1 (20%)	1/0	3 (25%)	2/0	20 (34%)
Dehydration	4 (29%)	-	5 (42%)	1/0	5 (31%)	-	3 (60%)	1/0	2 (17%)	-	19 (32%)
Dyspnea	5 (36%)	-	3 (25%)	-	7 (44%)	1/0	1 (20%)	-	2 (17%)	-	18 (31%)
Abdominal pain	6 (43%)	-	2 (17%)	1/0	6 (38%)	1/0	-	-	2 (17%)	1/0	16 (27%)
Headache	2 (14%)	-	3 (25%)	1/0	3 (19%)	-	1 (20%)	-	7 (58%)	-	16 (27%)
Alopecia	-	-	5 (42%)	-	5 (31%)	-	2 (40%)	-	3 (25%)	-	15 (25%)
Constipation	5 (36%)	-	5 (42%)	-	7 (44%)	-	-	-	1 (8%)	-	15 (25%)

Arm 1: cediranib+mFOLFOX6; arm 2: cediranib+docetaxel; arm 3A: cediranib+irinotecan; arm 3B: cediranib + irinotecan and cetuximab; arm 4: cediranib+pemetrexed

Table 3

Pharmacokinetic data, cediranib pharmacokinetic data following multiple doses (cycle 2, day 1) and chemotherapy pharmacokinetic data alone (cycle 1, day 1), and in combination (cycle 2, day 1) with cediranib

Cediranib pharmacokinetic data following multiple doses (cycle 2, day 1)

	Cediranib dose (mg)	n	Multiple-dose pharmacokinetic parameters		
			$C_{ss,max}$ (ng/mL)[a]	t_{max} (h)[b]	AUC_{ss} (ng/mL•h)[a]
Arm 1	20	5	65.3 (86.2)	4.0 (2.0, 6.0)	986 (98.8)
Arm 2	30	8	62.5 (53.3)	5.0 (0.5, 23.0)	1099 (59.2)
Arm 3A	20	5	76.0 (57.6)	2.1 (2.0, 5.9)	1014 (54.8)
Arm 3B	20	3	50.9 (126)	4.0 (2.0, 4.3)	668 (124)
Arm 4	30	4	74.9 (31.6)	4.0 (2.0, 4.0)	1206 (35.3)
Trial 2171IL0001 (single-agent cediranib)	20	11	66.6 (52.9)	3.0 (2.0, 6.4)	774 (51.6)
	30	12	69.6 (49.5)	2.1 (1.0, 4.0)	741 (48.7)

Chemotherapy pharmacokinetic data alone (cycle 1, day 1) and in combination (cycle 2, day 1) with cediranib

	Treatment period	Cediranib dose (mg)	Multiple-dose pharmacokinetic parameters			
			C_{max}		AUC	
			n	(ng/mL)[a]	n	(ng/mL•h)[a]
Arm 1	Oxaliplatin alone[c]	20/30	13	3300 (17.9)	13	71400 (28.2)[d]
	Oxaliplatin combination	20/30	9	3760 (26.0)	9	87000 (23.6)[d]
	5-FU alone	20/30	13	544 (72.9)	NA	NA
	5-FU combination	20/30	8	825 (86.5)	NA	NA
Arm 2	Docetaxel alone	30/45	11	2760 (32.0)	11	3770 (37.3)
	Docetaxel combination	30/45	9	3230 (42.0)	8	4460 (44.7)
Arm 3A	Irinotecan alone	20/30/45	16	3290 (21.1)	16	20400 (29.2)
	Irinotecan combination	20/30/45	11	3910 (35.2)	11	22800 (32.3)
	SN38 alone	20/30/45	16	35.4 (50.1)	9	595 (53.5)
	SN38 combination	20/30/45	11	38.7 (38.9)	6	711 (25.0)
Arm 3B	Irinotecan alone	20	5	3040 (18.3)	5	20300 (29.0)
	Irinotecan combination	20	4	3790 (23.7)	4	27700 (44.9)
	SN38 alone	20	5	29.1 (21.0)	3	482 (22.3)

Chemotherapy pharmacokinetic data alone (cycle 1, day 1) and in combination (cycle 2, day 1) with cediranib

	Treatment period	Cediranib dose (mg)	Multiple-dose pharmacokinetic parameters			
			C_{max}		AUC	
			n	(ng/mL)[a]	n	(ng/mL•h)[a]
	SN38 combination	20	4	35.1 (40.0)	4	583 (54.3)
Arm 4	Pemetrexed alone	30/45	7	180 (14.2)[e]	10	295 (37.7)[e]
	Pemetrexed combination	30/45	6	182 (44.3)[e]	7	264 (21.8)[e]

AUC, area under the plasma concentration-time curve; AUC_{SS}, area under the plasma concentration-time curve at steady state; C_{max}, maximum plasma concentration; C_{ssmax}, maximum steady-state drug concentration during dosing interval; tmax, time to reach peak or maximum concentration following drug administration

Arm 1: cediranib+mFOLFOX6; arm 2: cediranib+docetaxel; arm 3A: cediranib+irinotecan; arm 3B: cediranib + irinotecan and cetuximab; arm 4: cediranib+pemetrexed

[a] Values represent the geometric mean and CV% in parentheses;

[b] values represent the median value and the range in parentheses

[c] Oxaliplatin was quantified as total platinum;

[d] for oxaliplatin, due to the prolonged terminal phase half-life of platinum, only the area under the curve from zero to the last quantifiable concentration could be accurately estimated;

[e] units for pemetrexed C_{max} are u.g/mL and for AUC u.g.h/mL

Table 4

Tumor assessment (RECIST)

Cediranib dose, mg(n)	**Arm 1**		**Arm 2:**		**Arm 3A:**			**Arm 3B**	**Arm 4:**	
	20 (6)	**30 (5)**	**30 (7)**	**45 (3)**	**20 (5)**	**30 (5)**	**45 (1)**	**20 (4)**	**30 (7)**	**45 (3)**
Partial response	-	-	1	-	-	1	-	1	1	-
Stable disease[a]	4	3	4	1	3	2	1	2	4	2
Disease progression	1	2	-	-	2	-	-	-	-	-
Not evaluable	1	-	2	2	-	2	-	1	2	1
Total	6	5	7	3	5	5	1	4	7	3

[a] ≥6 weeks with no progression Arm 1: cediranib+mFOLFOX6; arm 2: cediranib+docetaxel; arm 3A: cediranib+irinotecan; arm 3B: cediranib + irinotecan and cetuximab; arm 4: cediranib+ pemetrexed