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Cediranib

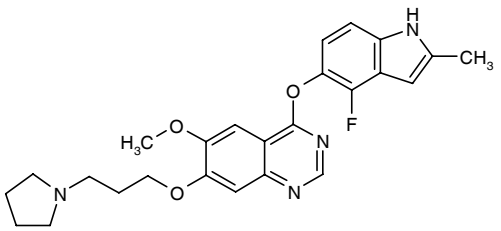
Rec INN

VEGFR Inhibitor
Antiangiogenic Agent
Oncolytic

AZD-2171
Recentin™

4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-6-methoxy-7-[3-(1-pyrrolidinyl)propoxy]quinazoline

InChI=1/C25H27FN4O3/c1-16-12-17-19(29-16)6-7-21(24(17)26)33-25-18-13-22(31-2)23(14-20(18)27-15-28-25)32-11-5-10-30-8-3-4-9-30/h6-7,12-15,29H,3-5,8-11H2,1-2H3



$C_{25}H_{27}FN_4O_3$
Mol wt: 450.5054

CAS: 288383-20-0
EN: 311106

Abstract

Angiogenesis is a complex biological event in which vascular endothelial growth factor (VEGF) is considered the rate-limiting step. VEGF mediates both physiological and pathological angiogenesis via binding to specific transmembrane receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR or Flk-1), expressed mainly on vascular endothelial cells. Because angiogenesis in healthy adults is generally absent, interruption of VEGF signaling is an attractive strategy to selectively inhibit angiogenesis in solid tumors. Antagonism of VEGFR-2 has attracted particular attention due to the generally limited expression of this receptor in endothelium and the crucial role it plays in VEGF-mediated angiogenic signaling. Cediranib (AZD-2171, Recentin™) is a novel, orally available quinazoline VEGFR inhibitor that was shown to potently inhibit VEGFR-1, VEGFR-2 and VEGFR-3 tyrosine kinase activity and VEGF-mediated signaling *in vitro* and *in vivo*. Cediranib exerted marked anticancer effects *in vivo* in a variety of xenograft models and in patients with advanced solid tumors. It continues to undergo clinical testing alone and in combination with selected chemotherapies for the oral treatment of various cancers.

Synthesis

Cediranib can be synthesized as follows:

Vanillic acid (I) is condensed with 1-(3-chloropropyl)-pyrrolidine (II) by means of K_2CO_3 and KI in hot DMF yielding 3-methoxy-4-[3-(1-pyrrolidinyl)propoxy]benzoic acid (III), which is nitrated with fuming HNO_3 in TFA to afford the *ortho*-nitrobenzoic acid (IV). Subsequent chlorination of acid (IV) with $SOCl_2$, followed by reaction with ammonia in THF/CH_2Cl_2, leads to the corresponding benzamide (V), which is reduced at the nitro group by means of Fe/HCl, providing the expected *ortho*-aminobenzoic acid (VI). The cyclization of (VI) with Gold's reagent (VII) in dioxane gives the quinazolinone (VIII), which is converted to the 4-chloroquinazoline (IX) upon treatment with $SOCl_2$ in the presence of a catalytic amount of DMF. Cediranib is finally obtained by condensation of chloroquinazoline (IX) with 4-fluoro-5-hydroxy-2-methylindole (X) in the presence of K_2CO_3 in hot DMF (1, 2). Scheme 1.

The intermediate 4-fluoro-5-hydroxy-2-methylindole (X) can be prepared by three alternative methods. The condensation of 2-fluoro-4-nitroanisole (XI) with 4-chlorophenoxyacetonitrile (XII) by means of potassium *tert*-butoxide produces a regioisomeric mixture of *ortho*-nitroarylacetonitriles (XIIIa) and (XIIIb) which, without separation, are reductively cyclized to indoles (XIVa) and (XIVb) by catalytic hydrogenation over Pd/C. After protection of indoles (XIV) as the respective *N*-Boc derivatives (XVa) and (XVb), metalation with *tert*-butyllithium followed by treatment with iodomethane yields the corresponding 1-Boc-2-methylindoles, which are further deprotected to (XVIa) and (XVIb) utilizing TFA. Demethylation of the mixture of methoxyindoles (XVI) with BBr_3 in cold CH_2Cl_2 leads to the analogous hydroxyindoles, which are separated by column chromatography to provide the target 4-fluoro-5-hydroxy-2-methylindole (X) (2). In a differ-

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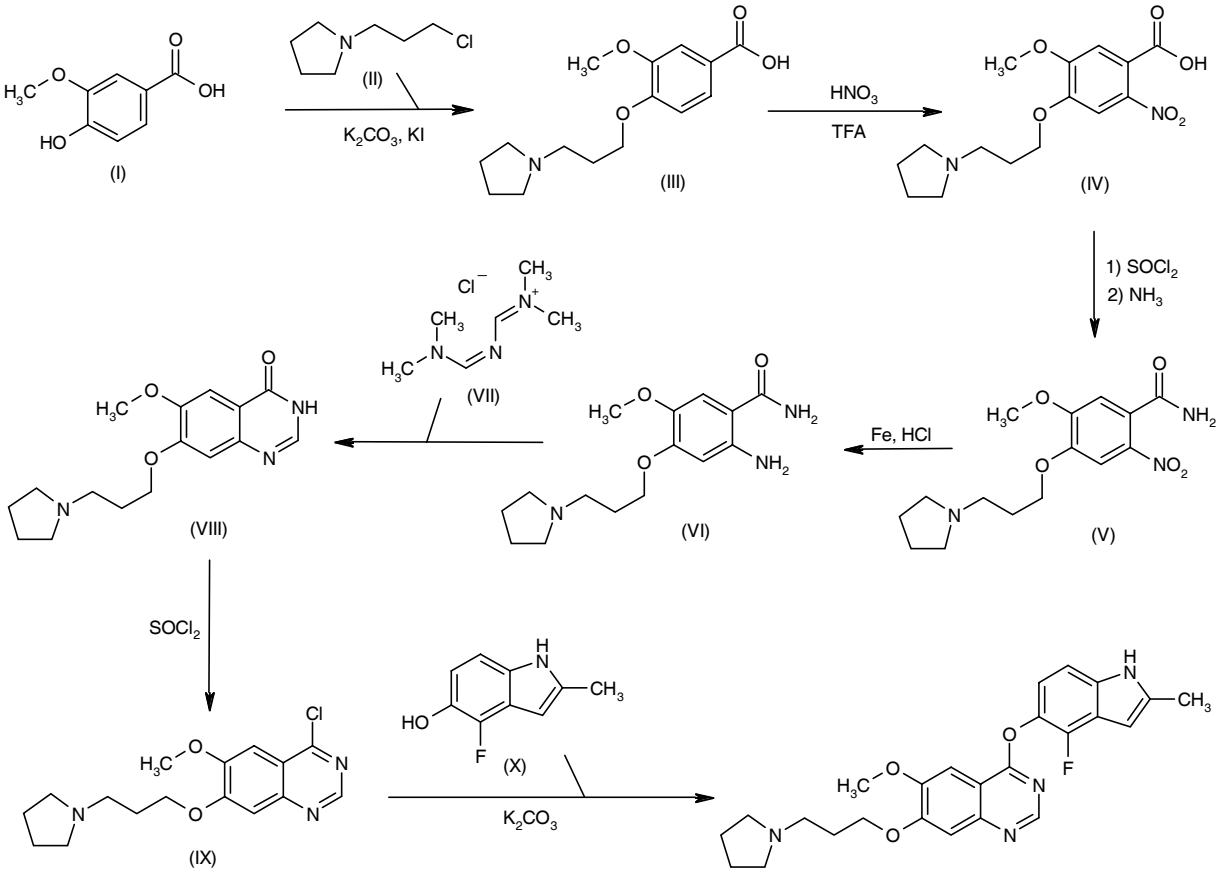
Scheme 1: Synthesis of Cediranib



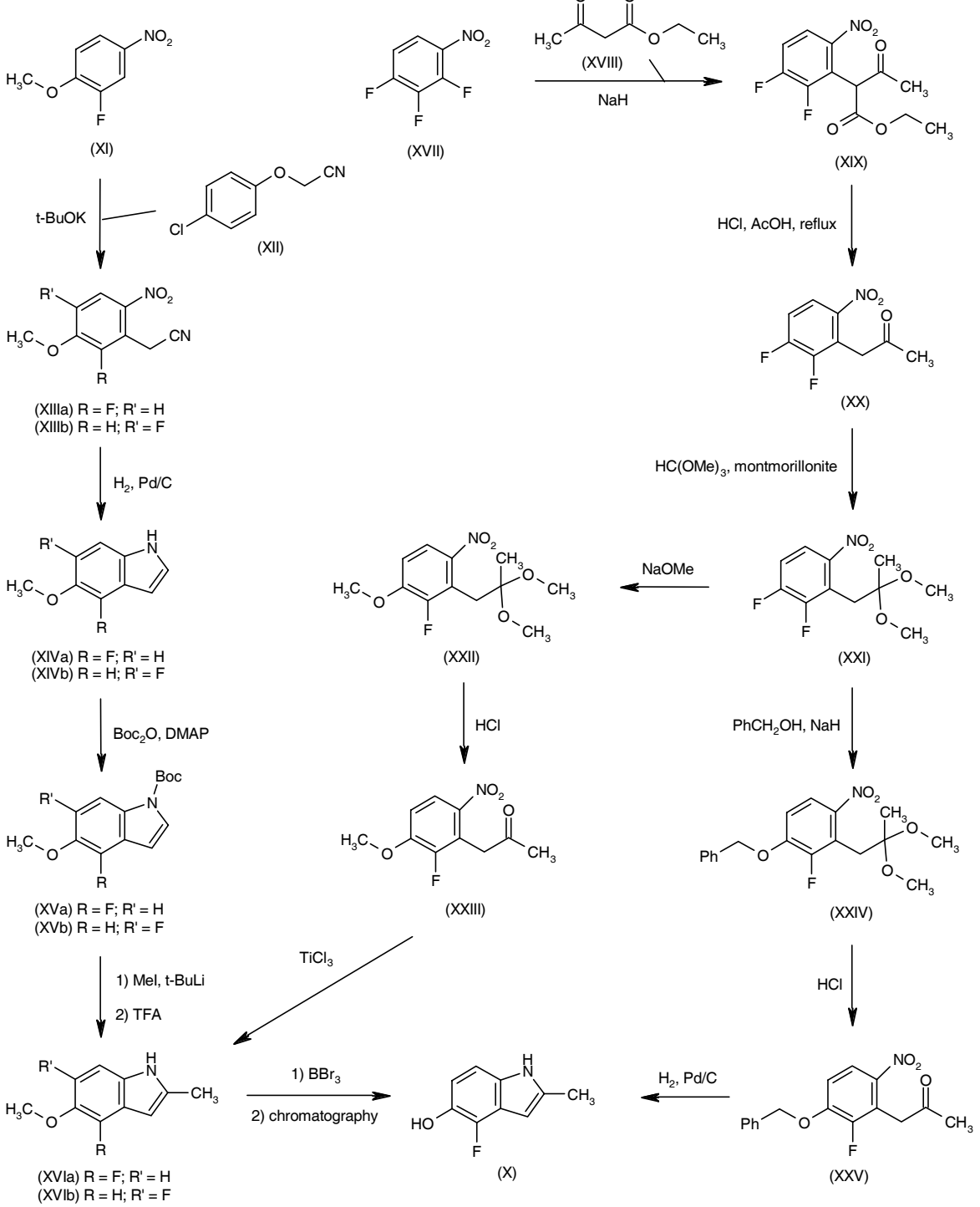
ent method, 2,3,4-trifluoronitrobenzene (XVII) is condensed with ethyl acetoacetate (XVIII) by means of NaH in THF followed by chromatographic separation of the resulting regioisomeric mixture to provide the 2-aryl acetoacetate (XIX). After acidic decarboxylation of (XIX), the obtained arylacetone derivative (XX) is protected as the dimethyl ketal (XXI) with trimethyl orthoformate and montmorillonite K10. Selective displacement of one fluoride group in (XXI) with sodium methoxide in methanol affords 1-(2-fluoro-3-methoxy-6-nitrophenyl)acetone dimethyl ketal (XXII), which is hydrolyzed to ketone (XXIII) under acidic conditions. The reductive cyclization of (XXIII) by means of $TiCl_3$ and ammonium acetate provides 4-fluoro-5-methoxy-2-methylindole (XVIa), which is demethylated to (X) by using BBr_3 as above (1, 2). Alternatively, the difluorophenyl ketal (XXI) is displaced with benzyl alcohol in the presence of NaH to give the benzyl ether (XXIV), which undergoes further ketal hydrolysis to the ketone (XXV) under acidic conditions. Finally, simultaneous cyclization and deprotection of (XXV) with H_2 and Pd/C furnishes the desired 4-fluoro-5-hydroxy-2-methylindole (X) (2). Scheme 2.

Background

Angiogenesis is an extremely complex biological event which involves integration of multiple signaling pathways to activate endothelial and perivascular cells and modify surrounding basement membranes and extracellular matrix. Although numerous and diverse factors are involved in this process, vascular endothelial growth factor (VEGF) is considered the rate-limiting step. VEGF is a secreted cytokine that induces both physiological and pathological angiogenesis. It is essential for blood vessel growth during embryonic development and also in some angiogenic pathologies in adults, including the progression of solid tumor growth and metastasis. VEGF stimulates endothelial cells to secrete proteases and plasminogen activators, which cause degradation of vessel basement membranes, allowing cells to invade the surrounding matrix and eventually differentiate to form a new lumen-containing vessel (3-5).

VEGF induces neovascularization and increases vascular permeability via binding to specific transmembrane receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR or Flk-1),

Scheme 2: Synthesis of Intermediate (X)



expressed mainly on vascular endothelial cells, as well as to the VEGF-C and VEGF-D receptor, VEGFR-3 (FLT4), expressed on lymphatic endothelium. Binding of the cytokine to these receptors initiates homo- or heterodimerization, which stimulates intrinsic kinase activity and subsequent transphosphorylation of tyrosine residues within the cytoplasmic domain. These phosphorylated residues are the recognition sites for Src homology 2 (SH2) domain-binding proteins, which are responsible for the propagation of intracellular signaling. VEGFR

activation can result in mitogenic (activation of the phospholipase C-γ [PLC-γ]/protein kinase C [PKC]/Raf/mitogen-activated protein kinase [MAPK] pathway), motogenic (FAK and paxillin phosphorylation) and survival signaling (complexed with VE-cadherin, β-catenin and phosphatidylinositol 3'-kinase [PI3K]) (5-11).

Angiogenesis in healthy adults is generally absent, with the exception of cyclical modifications in female reproductive tissues and longitudinal bone extension. Thus, for years, researchers have recognized the therapeutic potential of interruption of VEGF signaling to selectively inhibit solid tumor angiogenesis. Particular emphasis has been placed on antagonism of VEGFR-2, since its expression is generally limited to the endothelium and it is responsible for VEGF-mediated angiogenic signaling. Several inhibitors of VEGF signaling have been described, with more than 30 VEGFR-2 inhibitors under active development for the treatment of solid tumors (12-22).

One such novel VEGFR-2 inhibitor is the orally available quinazoline cediranib (AZD-2171, Recentin™). The agent was shown to potently inhibit VEGFR-1, VEGFR-2 and VEGFR-3 tyrosine kinase activity and VEGF-mediated signaling *in vitro* and *in vivo*. Cediranib exhibited potent anticancer and antivascular effects *in vivo* in several xenograft models and was chosen for further development for the oral treatment of various cancers (1, 23).

Preclinical Pharmacology

The inhibitory activity of cediranib was examined against several recombinant tyrosine kinases. Potent and highly selective activity was demonstrated against VEGFR-2 (IC_{50} < 1 nM), with activity also observed against VEGFR-1 and VEGFR-3 (IC_{50} = 5 and 3 nM or less, respectively). Cediranib inhibited the structurally related recombinant platelet-derived growth factor receptor (PDGFR)-related kinases, including c-Kit and PDGFRβ tyrosine kinase (IC_{50} = 2 and 5 nM, respectively). Activity was also noted against other PDGFR-related kinases, although it was > 36-fold more selective for VEGFR-2 than for PDGFRα and > 1,000-fold more selective for VEGFR-2 than for FLT3. The selectivity of cediranib for VEGFR-2 was superior relative to unrelated tyrosine kinases and serine/threonine kinases, such as epidermal growth factor receptor (EGFR; > 1,600-fold selectivity) and MEK (*i.e.*, the upstream activator of ERK [extracellular signal-regulated kinase]; > 10,000-fold selectivity). Cediranib had no effect against AMPK (AMP-activated protein kinase), Chk1 (checkpoint kinase 1), c-Jun *N*-terminal kinase (JNK), MAPK2, MSK1 (mitogen- and stress-activated kinase 1), PKA (protein kinase A), Akt/PKB, PKCα, ROCK2 (rho-associated coiled-coil-containing protein kinase 2), SAPK2b (stress-activated protein kinase 2b), SAPK2c, SGK (serum/glucocorticoid-regulated kinase), CSK (casein kinase) or PI3K (23).

Cediranib was also shown to potently and concentration-dependently inhibit VEGF-induced phosphorylation of VEGFR-2 (IC_{50} = 0.0005 μM) in human umbilical vein endothelial cells (HUVECs). In contrast, 10-16-fold higher concentrations of cediranib were required to inhibit PDGFRα and PDGFRβ phosphorylation in human osteosarcoma MG-63 cells. Cediranib displayed 420-20,000-fold selectivity for inhibition of VEGFR-2 phosphorylation as compared to CSF-1R (macrophage colony-stimulating factor 1 receptor), FLT3, EGFR and erbB-2. In addition, the agent markedly inhibited VEGF-induced HUVEC proliferation (IC_{50} = 0.0004 μM) more potently than other VEGFR tyrosine kinase inhibitors currently under clinical development, including vatalanib (IC_{50} = 0.008 μM), sunitinib (IC_{50} = 0.04 μM) and CP-547632 (IC_{50} = 0.06 μM). Moreover, cediranib displayed 275- and 1,250-fold selectivity for inhibition of VEGF-induced HUVEC proliferation *versus* basic fibroblast growth factor (bFGF)- and EGF-induced HUVEC proliferation, respectively (23, 24).

As mentioned above, cediranib exhibited potent activity against recombinant c-Kit tyrosine kinase. Further experiments using small cell lung cancer (SCLC; NCI-H526) and acute myeloid leukemia (AML; M07e and Kasumi-1) cell lines showed that the agent potently inhibited stem cell factor (SCF)-induced phosphorylation of c-Kit (IC_{50} = 2 nM or less) and concomitant downstream MAPK phosphorylation (25).

Cediranib inhibited angiogenesis both *in vitro* and *in vivo*. In experiments using co-cultures of HUVECs and human diploid fibroblasts, the agent inhibited vessel branching, length and area with IC_{50} values of 0.0001, 0.0001 and 0.0002 μM, respectively. VEGF-induced vessel formation in athymic BALB/c mice implanted s.c. with VEGF-containing Matrigel plugs was completely suppressed in animals treated with cediranib (1.5 and 6 mg/kg/day p.o. starting on the day of implantation and continuing for 7 days). Further evidence of its potent antiangiogenic activity was obtained in experiments in rats. Cediranib prevented further ossification of tibial and femoral growth plates of growing female rats and dose-dependently increased the zone of hypertrophy. Oral doses of 1.25, 2.5 and 5 mg/kg/day (for 28 days) increased epiphyseal growth plate area by 36%, 283% and 481%, respectively. Complete reversal of this effect was seen following a 28-day washout period. Moreover, development of the corpus luteum is a VEGF-dependent process and chronic administration of cediranib (5 mg/kg/day p.o. for 28 days) to female rats reduced the ovarian luteal area by 67% as compared to controls (23).

Cediranib directly inhibited the proliferation of a wide range of human tumor cells *in vitro*, but only at micromolar concentrations. IC_{50} values for the agent against ovarian adenocarcinoma (SK-OV-3), mammary adenocarcinoma (MDA-MB-231), prostate adenocarcinoma (PC-3), NSCLC (Calu-6) and colorectal carcinoma (SW620) cell lines were 3.0 ± 0.4, 3.8 ± 0.5, 5.8 ± 0.2, 6.4 ± 0.6 and 7.4 ± 0.4 μM, respectively. The concentrations were between 7,500- and 18,500-fold greater than those required for inhibition of VEGF-induced HUVEC proliferation. It was more potent against gastric cancer cells overexpressing an active form of K-SAM/FGFR2 (IC_{50} = 150 nM), although this concentration was 300-fold higher than that

required to inhibit VEGF-induced HUVEC proliferation; little activity was seen against other gastric cancer cells (23, 24, 26).

Cediranib displayed antitumor activity in several human tumor xenograft models. Using the Pediatric Preclinical Testing Program (PPTP) panel, cediranib was shown to induce significant growth delays in 83% of the tumor xenografts tested when administered at a dose of 6 mg/kg/day p.o. for 6 weeks. Intermediate effects were observed against 4 of 5 rhabdomyosarcoma, 3 of 3 Ewing sarcoma and 2 of 3 Wilms tumor xenografts. Complete responses were obtained against 1 of 3 rhabdoid, 1 of 3 osteosarcoma and 1 of 3 Wilms tumor xenografts, and chronic treatment (6 mg/kg/day for 21 days) of mice bearing established human lung tumor Calu-6 xenografts resulted in 68% inhibition of tumor growth. However, cediranib had no effect on the growth of acute lymphocytic leukemia (ALL) xenografts (23, 27).

Treatment of MMTV-*neu* transgenic mice (which spontaneously develop multiple mammary tumors) with cediranib from 14 to 19 weeks of age (0.75-6 mg/kg/day p.o.) resulted in significant, dose-dependent reductions in tumor burden; although treatment restricted tumor growth, the number of tumor foci was not affected, consistent with an antiangiogenic mechanism. Cediranib was also effective against well-established tumors (0.4 cm^3) in this same mouse model, where once-daily oral administration for 6 weeks induced dose-dependent tumor growth inhibition and doses of 3 and 6 mg/kg/day caused tumor regression (28).

Cediranib (5 mg/kg once daily for 28 days starting when mice were 6 weeks old) markedly inhibited early adenoma development in the $Apc^{Min/+}$ mouse model of early intestinal cancer. Treatment decreased the number of macroscopic polyps in the small bowel and colon. In addition, a significant reduction in the number of larger micropolyps in the small intestine was observed. Although late administration of cediranib (starting at 10 weeks of age) did not decrease polyp number, a significant decrease in polyp diameter was observed in the small bowel; no significant effect was observed on macroscopic polyps in the colon. Examination of intestinal tissue revealed that treatment with the agent significantly reduced the number of cells expressing VEGFR-2 mRNA; microvessel density and β-catenin staining in adenomas and nontumor tissue were unaffected by treatment (29).

Acute cediranib treatment (3 mg/kg p.o. x 2) of mice bearing s.c. SW620 colorectal carcinoma xenografts significantly reduced tumor vascular volume by 68% and permeability by 80%. In experiments using mice bearing murine renal cell carcinoma (RENCA) cells, primary tumor volume, lung metastasis and primary tumor microvessel density were also significantly reduced (50-58%, 54% and 45-70%, respectively) following treatment with cediranib (6.3 mg/kg/day p.o. for 11 or 7 days starting 10 or 8 days, respectively, postimplantation) (30, 31).

Experiments using an orthotopic human lung adenocarcinoma (NCI-H441) model in mice demonstrated that the antitumor and antivascular effects of cediranib (6 mg/kg/day p.o. starting 5 days postimplantation) were enhanced when it was combined with gefitinib (25 mg/kg/day p.o.) or paclitaxel (150 μg/week i.p.). Reductions in tumor growth, lymphatic and chest wall metastasis and pleural effusion were greater with the combinations as compared to treatment with any of the agents alone. Moreover, combination treatment markedly decreased lung primary tumor microvessel density and cell proliferation and levels of VEGF, basic fibroblast growth factor (bFGF), transforming growth factor-α (TGF-α), interleukin-8 (IL-8) and the matrix metalloproteinases MMP-2 and MMP-9 (32).

A study using athymic mice implanted with human breast cancer MCF7 cells transfected with vector ($MCF7^{neo}$) or VEGF (MCF^{VEGF}) in mammary fat pads showed that treatment with cediranib (5 mg/kg/day) significantly decreased established $MCF7^{neo}$ tumor growth and caused regression of MCF^{VEGF} tumors. A significant reduction in blood flow, microvessel density and proliferation was also observed in MCF^{VEGF} tumors at 24 h (33).

Several studies have reported that cediranib also acts as a radiation enhancer, improving tumor growth delays in a number of models, including lung cancer NCI-H460 and Calu-6, colorectal cancer LoVo and head and neck cancer CAL33 human tumor xenograft mouse models. Inhibition of tumor proliferation and promotion of apoptosis were enhanced when fractionated radiation was combined with cediranib therapy as compared to either treatment alone (34-37).

Pharmacokinetics and Metabolism

In early pharmacokinetic studies performed in rats, cediranib exhibited a half-life of 9 h, low clearance and good oral bioavailability (F > 40%) (1).

The pharmacokinetics of cediranib (1, 2.5, 5, 10, 20 and 30 mg p.o. once daily) were examined in a phase I trial conducted in 24 patients with hormone-refractory prostate cancer (HRPC). Data obtained from 18 evaluable patients showed linear pharmacokinetics with no time-dependent changes. The time to plasma C_{max} ranged from 2 to 8 h and the mean half-life was about 20 h. At steady state following multiple dosing at 20 mg, the unbound minimum plasma concentration was 5 times higher than the IC_{50} required to inhibit HUVEC proliferation. Efficacy and safety data from this trial are presented below (38-40).

In a phase I clinical trial in patients with advanced refractory solid tumors described below (41), the terminal half-life for single-dose cediranib (0.5-60 mg) was 12.5-35.4 h and plasma levels increased linearly after both single and multiple doses.

Safety

The tolerability and safety of cediranib (starting dose of 30 mg once daily p.o. starting on day 3 of cycle 1) combined with modified FOLFOX6 (oxaliplatin 85 mg/m^2 over 2 h, leucovorin 400 mg/m^2 over 2 h and 5-FU 400 mg/m^2

by bolus followed by 2400 mg/m^2 by continuous infusion over 46 h) in cycles of 14 days were examined in a phase I study in patients with locally advanced or metastatic colorectal cancer (CRC) and no prior chemotherapy for advanced disease. Results from 9 patients receiving 16 cycles were analyzed. The most common adverse events were diarrhea, fatigue, nausea and hypertension, which appeared to be manageable. One case of dose-limiting grade 3 diarrhea was seen in a patient at 30 mg. All hematological toxicities were similar to those expected with mFOLFOX6 alone (42).

Clinical Studies

The above-mentioned phase I trial in HRPC also assessed the tolerability, safety and efficacy of cediranib. Only mild adverse events, the most common being fatigue (n=5), anorexia (n=3) and nausea (n=3), were reported at doses of 10 mg or less. Possibly drug-related grade 3 hypertension (n=2), fatigue (n=1), muscular weakness (n=1), myalgia (n=1) and transient ischemic attack (n=1) were seen at the 20- and 30-mg dose levels. Two patients in the 20-mg cohort experienced a decrease in prostate-specific antigen (PSA) from baseline of 30% and > 50%, respectively. The latter patient also exhibited resolution of adenopathy for more than 6 months with no further chemotherapy (38, 39). The results from this and most of the following studies are summarized in Table I.

A phase I trial in patients with advanced solid tumors and liver metastases examined the safety and efficacy of single doses of cediranib of 0.5-60 mg p.o., followed by a 7-day washout period and then daily treatment at the same doses on 28-day cycles. Cediranib was generally well tolerated at doses of 45 mg/day or less. The most common adverse events reported were fatigue (n=13), nausea (n=13), diarrhea (n=10) and vomiting (n=10). Serious events of grade 4 cerebral hemorrhage, grade 4 hypoglycemia and grade 3 hypertension developed in 1 patient each in the highest dose cohort, which were possibly related to study drug. Acute, dose-independent increases in VEGF and dose- and time-dependent decreases in soluble VEGFR-2 were observed. Of 36 patients enrolled at the time of reporting, 2 had unconfirmed partial responses at the highest dose and 3 minor responses at lower doses. Reduced tumor blood flow and permeability were observed in 2 of 3 patients at 20 mg and 3 of 4 patients at 45 mg (41).

The safety and efficacy of cediranib (30 or 45 mg p.o. starting on day 2 of cycle 1) in combination with carboplatin (AUC = 6) and paclitaxel (200 mg/m^2 over 3 h every 3 weeks) were investigated in a phase I trial in 20 patients with advanced NSCLC. One confirmed dose-limiting toxicity (DLT) of a grade 3 increase in alanine aminotransferase (ALT) was seen in a patient at 30 mg. Six patients developed hypertension of at least grade 2 that was manageable. One DLT of grade 3 febrile neutropenia with grade 3 mucositis was observed in a patient at 45 mg. Other frequent adverse events observed in all cohorts were fatigue, anorexia mucositis and diarrhea. Hematological toxicities were comparable to those associated with carboplatin + paclitaxel; no hemoptysis was seen. Of the 15 patients evaluable for response, 6 achieved a partial response, 8 had stable disease and 1 disease progression. Several of the patients with stable disease also exhibited tumor shrinkage with central cavitation (43, 44).

A 2-part phase I trial in patients with advanced solid tumors examined the safety and efficacy of once-daily cediranib (0.5-60 mg p.o. in part A; 20, 30 and 45 mg p.o. in part B). The agent was generally well tolerated at doses up to 45 mg/day. Initial efficacy results included dose-dependent decreases in hepatic lesions in 6 patients with CRC. Multiple doses of 20 mg appeared to be associated with target enzyme inhibition for over 24 h, and a dose- and exposure-dependent decrease in tumor blood flow was observed at all doses (0.5-60 mg) (45).

Another phase I study in patients with locally advanced or metastatic CRC and no prior chemotherapy for metastatic disease examined the efficacy, tolerability and safety of cediranib (30 mg/day, escalated to 45 mg/day once daily p.o. starting on day 8 of cycle 1) combined with capecitabine (1000 mg/m^2 b.i.d. for 14 days every 3 weeks). In the 9 patients enrolled at the time of reporting, the most common adverse events were generally grade 1 and 2 and included hand-foot syndrome, fatigue, diarrhea, rash, anorexia, dyspnea, nausea, mucositis and voice changes; grade 1 myelosuppression was also reported. No DLTs were seen and only 1 serious adverse event of grade 3 dehydration developed in cycle 3 at the dose of 45 mg. All 3 patients evaluable for response had stable disease (46).

A further phase I trial conducted in patients with advanced refractory tumors demonstrated the efficacy, safety and tolerability of cediranib (20, 25, 30 or 45 mg once daily p.o.) in combination with gefitinib (250 or 500 mg once daily) in 70 treated patients. The most common adverse events were diarrhea (91%), anorexia (64%), fatigue (51%) and cediranib dose-related hypertension (51%). Adverse events of grade 3 or greater occurred in < 13% of patients and included increases in ALT (7%) and aspartate aminotransferase (AST; 4%). Analysis of steady-state pharmacokinetics at a cediranib dose of 30 mg and a gefitinib dose of 250 mg showed no significant drug interactions. A total of 28 patients had stable disease; 22 were not evaluable for response. Confirmed partial responses were seen in 1 patient with mesothelioma at 45 mg cediranib + 250 mg gefitinib and another patient with renal cancer at 20 mg cediranib + 500 mg gefitinib. The latter patient underwent surgery and continues to be disease-free (47).

The tolerability and efficacy of escalating doses of cediranib (20, 30 and 45 mg p.o.) in combination with mFOLFOX6 (85 mg/m^2 oxaliplatin, 400 mg/m^2 5-FU and 400 mg/m^2 leucovorin every 2 weeks), irinotecan (300 mg/m^2 every 3 weeks), docetaxel (75 mg/m^2) or pemetrexed (500 mg/m^2) were examined in a phase I trial in 46 heavily pretreated patients with advanced solid tumors. Of the 35 patients evaluable for toxicity, 2 DLTs were observed in 8 patients receiving 30 mg cediranib +

Table I: Clinical studies of cediranib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions/objectives	Ref.
Cancer, prostate	Open Multicenter	Cediranib, 1 mg o.d. p.o. (n=3) Cediranib, 2.5 mg o.d. p.o. (n=3) Cediranib, 5 mg o.d. p.o. (n=3) Cediranib, 10 mg o.d. p.o. (n=3) Cediranib, 20 mg o.d. p.o. (n=10) Cediranib, 30 mg o.d. p.o. (n=2)	24	Cediranib at doses of up to 20 mg/d was well tolerated in patients with hormone-refractory prostate cancer	38-40
Cancer, metastatic (to liver)	Open	Cediranib, 0.5 mg p.o. → Washout x 7 d → Cediranib, 0.5 mg p.o. o.d. x 28 d (n=3) Cediranib, 1 mg p.o. → Washout x 7 d → Cediranib, 1 mg p.o. o.d. x 28 d (n=3) Cediranib, 2.5 mg p.o. → Washout x 7 d → Cediranib, 2.5 mg p.o. o.d. x 28 d (n=3) Cediranib, 5 mg p.o. → Washout x 7 d → Cediranib, 5 mg p.o. o.d. x 28 d (n=3) Cediranib, 10 mg p.o. → Washout x 7 d → Cediranib, 10 mg p.o. o.d. x 28 d (n=4) Cediranib, 20 mg p.o. → Washout x 7 d → Cediranib, 20 mg p.o. o.d. x 28 d (n=3) Cediranib, 30 mg p.o. → Washout x 7 d → Cediranib, 30 mg p.o. o.d. x 28 d (n=5) Cediranib, 45 mg p.o. → Washout x 7 d → Cediranib, 45 mg p.o. o.d. x 28 d (n=4) Cediranib, 60 mg p.o. → Washout x 7 d → Cediranib, 60 mg p.o. o.d. x 28 d (n=8)	36	Continuous once-daily cediranib was well tolerated at doses up to 45 mg/day in patients with advanced solid tumors metastatic to the liver	41
Cancer, colorectal	Open	Oxaliplatin, 85 mg/m^2 i.v. infusion over 2 h on d 1 + Leucovorin, 400 mg/m^2 i.v. infusion over 2 h on d 1 + 5-Fluorouracil, 400 mg/m^2 i.v. bolus → 2400 mg/m^2 i.v. infusion over 46 h on d 1-2 → Cediranib, 30 mg/d p.o. on d 3 1x/2 wks	9	Cediranib + FOLFOX6 (oxaliplatin, leucovorin and 5-fluorouracil) was associated with manageable toxicity in patients with advanced or metastatic colorectal cancer	42
Cancer, lung (non-small cell)	Open	Carboplatin, AUC 6 i.v. + Paclitaxel, 200 mg/m^2 i.v. infusion over 3 h 1x/21 d + Cediranib, 30 mg p.o. o.d. on d 2-21 (n=9) Carboplatin, AUC 6 i.v. + Paclitaxel, 200 mg/m^2 i.v. infusion over 3 h 1x/21 d + Cediranib, 45 mg p.o. o.d. on d 2-21 (n=11)	20	The combination of cediranib, carboplatin and paclitaxel demon strated antitumor activity and an acceptable toxicity profile in patients with advanced non-small cell lung cancer. Cediranib reduced paclitaxel and increased carboplatin clearance at higher doses	44, 86
Cancer	Open	Cediranib, 0.5-60 mg p.o. o.d. Cediranib, 20 mg p.o. o.d. Cediranib, 30 mg p.o. o.d. Cediranib, 45 mg p.o. o.d.		Cediranib was well tolerated at doses up to 45 mg/day and appeared to be associated with broad antitumor activity, particularly in patients with advanced colorectal cancer. Pharmacokinetics were supportive of once-daily dosing	45
Cancer, colorectal	Open	Cediranib, 30 mg p.o. o.d. on d 8-21 + Capecitabine, 1000 mg/m^2 b.i.d. x 14 d 1x/3 wks Cediranib, 45 mg p.o. o.d. on d 8-21 + Capecitabine, 1000 mg/m^2 b.i.d. x 14 d 1x/3 wks	9	The recommended doses of cediranib and capecitabine in patients with colorectal cancer were 45 mg/d and 1000 mg/m^2 twice daily, respectively	46
Cancer	Open	Cediranib, 20 mg p.o. o.d. + Gefitinib, 250 mg (n=3) Cediranib, 20 mg p.o. o.d. + Gefitinib, 500 mg (n=8) Cediranib, 25 mg p.o. o.d. + Gefitinib, 250 mg (n=5) Cediranib, 25 mg p.o. o.d. + Gefitinib, 500 mg (n=8) Cediranib, 30 mg p.o. o.d. + Gefitinib, 250 mg (n=15) Cediranib, 30 mg p.o. o.d. + Gefitinib, 500 mg (n=8) Cediranib, 45 mg p.o. o.d. + Gefitinib, 250 mg (n=8) Cediranib, 45 mg p.o. o.d. + Gefitinib, 500 mg (n=15)	70	The combination of cediranib and gefitinib had no unexpected toxicity and was associated with encouraging preliminary responses in patients with refractory advanced tumors	47

Continuation

Table I (Cont.): Clinical studies of cediranib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions/objectives	Ref.
Cancer	Open	Cediranib, 20 mg p.o. + Irinotecan, 300 mg/m^2 i.v. infusion over 90 min 1x/3 wks Cediranib, 30 mg p.o. + Irinotecan, 300 mg/m^2 i.v. infusion over 90 min 1x/3 wks Cediranib, 45 mg p.o. + Irinotecan, 300 mg/m^2 i.v. infusion over 90 min 1x/3 wks Cediranib, 20 mg p.o. + Docetaxel, 75 mg/m^2 i.v. infusion over 60 min 1x3 wks Cediranib, 30 mg p.o. + Docetaxel, 75 mg/m^2 i.v. infusion over 60 min 1x/3 wks Cediranib, 45 mg p.o. + Docetaxel, 75 mg/m^2 i.v. infusion over 50 min 1x3 wks Cediranib, 20 mg p.o. + Pemetrexed, 500 mg/m^2 i.v. infusion over 10 min 1x3 wks Cediranib, 30 mg p.o. + Pemetrexed, 500 mg/m^2 i.v. infusion over 10 min 1x/3 wks Cediranib, 45 mg p.o. + Pemetrexed, 500 mg/m^2 i.v. infusion over 10 min 1x/3 wks Cediranib, 20 mg p.o. + Oxaliplatin, 85 mg/m^2 i.v. infusion over 2 h + Leucovorin, 400 mg/m^2 i.v. infusion over 2 h + 5-Fluorouracil, 400 mg/m^2 i.v. bolus over 2-4 min → 2400 mg/m^2 infusion over 46 h 1x/2 wks Cediranib, 30 mg p.o. + Oxaliplatin, 85 mg/m^2 i.v. infusion over 2 h + Leucovorin, 400 mg/m^2 i.v. infusion over 2 h + 5-Fluorouracil, 400 mg/m^2 i.v. bolus over 2-4 min → 2400 mg/m^2 infusion over 46 h 1x/2 wks Cediranib, 45 mg p.o. + Oxaliplatin, 85 mg/m^2 i.v. infusion over 2 h + Leucovorin, 400 mg/m^2 i.v. infusion over 2 h + 5-Fluorouracil, 400 mg/m^2 i.v. bolus over 2-4 min → 2400 mg/m^2 infusion over 46 h 1x/2 wks	46	Preliminary results suggested that cediranib 30 mg combined with selected chemotherapy regimens was safe and well tolerated in patients with advanced solid tumors. There was evidence of antitumor activity even in patients who had previously received the same chemotherapy regimen without cediranib. Cediranib had no major influence on the pharmacokinetics of any concomitant chemotherapy agent tested in this study	48, 49
Cancer, colorectal, Cancer, lung (non-small cell)	Open Multicenter	Paclitaxel, i.v. on d 1 + Carboplatin, i.v. on d 1 1x/21 d + Cediranib, p.o. o.d. d 2-21 [course 1] → d 1-21 [subsequent courses] x 8 cycles Capecitabine, p.o. b.i.d. on d 1-14 1x/21 d + Cediranib, p.o. o.d. d 8-21 [course 1] → d 1-21 [subsequent courses] x 6 cycles	35	This phase I study will determine the maximum tolerated dose, safety profile, pharmacokinetics and antitumor activity of cediranib combined with standard chemotherapy with paclitaxel plus carboplatin or capecitabine in patients with non-small cell lung cancer and colorectal cancer	50
Cancer, lung (non-small cell) Cancer, head and neck	Randomized Double-blind Multicenter	Cediranib Gefitinib Cediranib + Gefitinib		This phase I study will provide information on the safety profile and antitumor effects of cediranib alone, gefitinib alone and both drugs combined in patients with head and neck cancer or non-small cell lung cancer	52
Cancer, colorectal, Cancer, lung (non-small cell)	Open Multicenter	Cediranib, p.o. o.d. [starting on d 2] + [non-small cell lung cancer] Cisplatin, i.v. on d 1 + Gemcitabine, i.v. on d 1 & 8 1x/21 d [until progression or unacceptable toxicity] or [colorectal cancer] Oxaliplatin, i.v. infusion over 2 h on d 1 + Leucovorin, i.v. infusion over 2 h on d 1 + 5-Fluorouracil, i.v. infusion over 46 h on d 1 & 2 1x/14 d [until progression or unacceptable toxicity]	30	A phase I study was initiated to evaluate the phamacokinetics, tolerability and best dose of cediranib in combination with standard chemotherapy for the treatment of advanced non-small cell lung cancer or colorectal cancer	53
Cancer	Open	Cediranib, p.o. o.d. x 28 d	33	This phase I study will determine the maximum tolerated dose, dose-limiting toxicity, pharmacodynamics and pharmacokinetics of cediranib in children and adolescents with refractory or recurrent solid tumors or acute myelogenous leukemia	54
Cancer, brain	Open Multicenter	Cediranib, p.o. o.d. x 28 d x 13 [max.] cycles	55	This phase I study will determine the maximum tolerated dose, safety and pharmacokinetics of cediranib in patients with recurrent, progressive or refractory primary central nervous system tumors	55

Continuation

Table I (Cont.): Clinical studies of cediranib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions/objectives	Ref.
Cancer	Randomized Double-blind	Cediranib, 30 mg x 12 wks Cediranib, 45 mg x 12 wks	120	This phase II study will determine the tolerability and efficacy of cediranib plus hypertension management strategy in patients with advanced cancer	58
Cancer, lung (non-small cell)	Open Multicenter	Cediranib, p.o. o.d. x 28 d + Pemetrexed, i.v. infusion over 10 min on d 8 1x/4 wks [course 1] → [subsequent courses] Cediranib, p.o. o.d. x 21 d + Pemetrexed, i.v. infusion over 10 min on d 1 1x/3 wks	74	This phase II study will assess the response rates, progression-free and overall survival of combined cediranib and pemetrexed in patients with relapsed non-small cell lung cancer	59
Cancer	Randomized Open	Cediranib, p.o.	60	This phase II study will determine the effects of food on single-dose cediranib (45 mg) and the efficacy of a fixed or individualized daily dose of the drug in patients with advanced solid tumors	60
Cancer, kidney (renal cell carcinoma) metastastic	Open Multicenter	Cediranib, p.o. o.d. x 4 wks	41	This phase II study will evaluate the antitumor effects and safety of cediranib in patients with refractory metastatic renal cell carcinoma	61
Cancer, breast metastatic	Open	Cediranib, p.o. o.d. x 42 d	26	This phase II study will determine the antitumor activity and tolerability of cediranib in patients with refractory metastatic breast cancer	62
Cancer, malignant mesothelioma	Open Multicenter	Cediranib, p.o. o.d. x 28 d	50	The antitumor activity and objective response rates of cediranib in patients with malignant mesothelioma will be evaluated in this phase II study	63
Cancer, gastro-intestinal (stromal)	Open Multicenter	Cediranib, 45 mg/d	25	This phase II study will assess the antitumor activity and biological effects of cediranib in patients with metastatic gastrointestinal stromal tumors (GISTs)	64
Cancer, colorectal metastatic	Randomized Double-blind Multicenter	Cediranib + 5-Fluorouracil + Leucovorin + Oxaliplatin Bevacizumab + 5-Fluorouracil + Leucovorin + Oxaliplatin	210	This phase II study will compare the antitumor effects of cediranib and bevacizumab, both combined with FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) in patients with metastatic colorectal cancer	65
Cancer, liver	Open	Cediranib, p.o. o.d. x 28 d	34	This phase II study will assess the safety and antitumor effects of cediranib in patients with metastatic or locally advanced unresectable liver cancer	70
Cancer, kidney (renal cell carcinoma)	Randomized Double-blind Multicenter	Cediranib, 45 mg/d x 12 wks Placebo	65	Using RECIST criteria, the safety and efficacy of cediranib in the treatment of metastatic or recurrent renal cell carcinoma, as well as the pharmacokinetic profile of the compound and its effect on biomarker levels, will be established in a phase II study initiated in January 2007	71
Cancer, breast	Open	Cediranib, p.o. o.d. x 42 d	26	This phase II study, initiated in September 2005, will assess the efficacy and tolerability of cediranib in patients with refractory stage IV breast cancer	72
Cancer, brain (glioblastoma)	Open	Cediranib, p.o. o.d. x 28 d	31	This trial started in February 2006 and will evaluate the antitumor effects and safety of cediranib in the treatment of recurrent glioblastoma	73
Cancer, malignant mesothelioma	Open Multicenter	Cediranib, p.o. o.d. x 28 d	40	This phase II study will determine the clinical benefits, overall survival and tolerability of cediranib in patients with unresectable malignant pleural mesothelioma	74

Continuation

Table I (Cont.): Clinical studies of cediranib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions/objectives	Ref.
Cancer, ovarian, Cancer, fallopian tube, Cancer, peritoneal	Open	Cediranib, p.o. o.d. x 28 d	71	The efficacy of cediranib in patients with recurrent ovarian, peritoneal and fallopian tube cancer will be determined in this phase II study	75
Cancer, kidney (renal cell carcinoma)	Open Multicenter	Cediranib, p.o. o.d. x 28 d	37	This phase II study will determine the tolerability and antitumor efficacy of cediranib in patients with locally recurrent or unresectable metastatic renal cell carcinoma	76
Cancer, fallopian tube, Cancer, ovarian, Cancer, peritoneal	Open Multicenter	Cediranib, p.o. o.d. x 28 d	64	This phase II study will determine the objective response rates of cediranib in patients with recurrent or refractory advanced ovarian epithelial, fallopian tube or peritoneal cavity cancer	77
Cancer, prostate metastatic	Open	Cediranib p.o. o.d. x 28 d	37	A phase II study will assess the antitumor activity of cediranib in patients with metastatic androgen-independent prostate cancer	80
Cancer, colorectal metastatic	Randomized Double-blind Multicenter	Cediranib + 5-Fluorouracil + Leucovirin + Oxaliplatin Bevacizumab + 5- Fluorouracil + Leucovorin + Oxaliplatin	1600	This phase II/III study will compare the safety and antitumor activity of cediranib and bevacizumab, both combined with FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) in patients with metastatic colorectal cancer	82
Cancer, lung (non-small cell)	Randomized Double-blind Multicenter	Cediranib, p.o. o.d. + Paclitaxel, i.v. infusion over 3 h + Carboplatin, i.v. infusion over 30 min 1x/21 d x 6-8 cycles Placebo + Paclitaxel, i.v. infusion over 3 h + Carboplatin, i.v. infusion over 30 min 1x/21 d x 6-8 cycles	750	This phase II/III study will evaluate the antitumor activity and tolerability of paclitaxel and carboplatin alone or combined with cediranib in patients with advanced or metastatic non-small cell lung cancer	83
Cancer, colorectal metastatic	Randomized Double-blind Multicenter	Cediranib + 5-Fluorouracil + Leucovorin + Oxaliplatin + Capectabine Placebo + 5-Fluorouracil + Leucovorin + Oxaliplatin + Capectabine	1050	This phase III study will evaluate the safety and efficacy of adding cediranib to combined chemotherapy with FOLFOX/XELOX (5-fluorouracil, leucovorin and oxaliplatin/capecitabine and oxaliplatin) in patients with previously untreated metastatic colorectal cancer	84
Neurofibromatosis	Open Multicenter	Cediranib, p.o. o.d. x 28 d	65	A phase II study was initiated to evaluate the efficacy, toxicity and effect on quality of life of cediranib in patients with type 1 neurofibromatosis and extensive plexiform and/or paraspinal neurofibroma	85

mFOLFOX6; an additional cohort of less heavily pretreated patients was added to further determine the tolerability of this combination regimen. DLTs reported were grade 3 fatigue in the cohorts receiving cediranib + mFOLFOX6, irinotecan or pemetrexed; grade 3 diarrhea in the cediranib + mFOLFOX6 group; grade 3 hand-foot syndrome and grade 4 neutropenic fever in the cediranib + irinotecan group; and grade 3 hypertension in the cediranib + pemetrexed group. No significant pharmacokinetic drug interactions were observed. In the 28 heavily pretreated patients evaluable for response, 2 complete responses, 6 partial responses, 5 minor responses and 6 disease stabilizations (for 4 cycles or more) were reported. Responses have been sustained for 4-22+ cycles (48, 49).

Cediranib continues to undergo phase I-III clinical development alone or in combination with selected chemotherapies for the treatment of various cancers, including colorectal, NSCLC, SCLC, breast, head and neck, kidney, liver, ovarian, prostate, gastrointestinal stromal cancer (GIST), glioblastoma multiforme, AML, melanoma, malignant mesothelioma, myelodysplasia and lymphoma. Cediranib is also undergoing phase II development for the treatment of the precancerous/nonmalignant neurofibromatosis type I (50-85).

Drug Interactions

The effects of cediranib on the pharmacokinetics of carboplatin and paclitaxel were also examined in the study in patients with advanced NSCLC (see Ref. 43, 44). Results from 18 patients after 2 cycles of treatment showed that paclitaxel clearance was significantly decreased by about 20% in cycle 2. In addition, carboplatin clearance significantly increased with the higher cediranib dose. Further studies are required to determine the clinical significance of these interactions (86).

Source

AstraZeneca (SE, UK, US).

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