

Efficacy, Safety, Pharmacokinetics, and Biomarkers of Cediranib Monotherapy in Advanced Hepatocellular Carcinoma: A Phase II Study

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Abstract

Purpose: We conducted a single-arm phase II study of cediranib, a pan-VEGFR tyrosine kinase inhibitor, in patients with advanced hepatocellular carcinoma (HCC).

Experimental Design: Patients with histologically confirmed measurable advanced HCC and adequate hematologic, hepatic, and renal functions received cediranib 30-mg orally once daily (4 weeks/cycle). The primary endpoint was progression-free survival (PFS) rate at 3 months. Other endpoints included response rates, overall survival (OS), pharmacokinetics (PK), and biomarkers for cediranib.

Results: Cediranib treatment resulted in an estimated 3-month PFS rate of 77% (60%, 99%). Median PFS was 5.3 (3.5, 9.7) months, stable disease was seen in 5/17 patients (29%), and median OS was 11.7 (7.5–13.6) months. Grade 3 toxicities included hypertension (29%), hyponatremia (29%), and hyperbilirubinemia (18%). Cediranib PK were comparable to those seen in cancer patients with normal hepatic function. Plasma levels of VEGF and PlGF increased and sVEGFR1, sVEGFR2, and Ang-2 decreased after cediranib treatment. PFS was inversely correlated with baseline levels of VEGF, sVEGFR2, and bFGF and with on-treatment levels of bFGF and IGF-1, and directly associated with on-treatment levels of IFN- γ . OS was inversely correlated with baseline levels of sVEGFR1, Ang-2, TNF- α , CAIX, and CD34⁺CD133⁺CD45^{dim} circulating progenitor cells and on-treatment levels of sVEGFR2.

Conclusions: Despite the limitations of primary endpoint selection, cediranib at 30-mg daily showed a high incidence of toxicity and preliminary evidence of antitumor activity in advanced HCC. Hepatic dysfunction did not seem to affect the steady-state PK of cediranib. Exploratory studies suggested proangiogenic and inflammatory factors as potential biomarkers of anti-VEGF therapy in HCC. *Clin Cancer Res*; 19(6); 1557–66. ©2013 AACR.

Introduction

Hepatocellular carcinoma (HCC) is the 6th most common cancer and the 3rd most common cause of cancer-related mortality worldwide (1). Two randomized phase III trials have showed that sorafenib—a multitargeted tyrosine kinase inhibitor (TKI)—improved survival in patients with

advanced HCC (2, 3). However, during the time since the FDA approval of sorafenib and its worldwide clinical application, it has become increasingly evident that the therapeutic benefits of sorafenib are relatively modest. Moreover, the actual mechanisms mediating the therapeutic effects or resistance to anti-VEGF therapy with TKIs, as well as their adverse effects remain unclear.

Emerging evidence supports the role of angiogenesis in hepatocarcinogenesis and suggests the potential for inhibiting this pathway as a therapeutic strategy in HCC (4–7). Excessive and abnormal vasculature, presumably because of upregulation of growth factors including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), is one of the hallmarks of HCC (8). It is possible that sorafenib exerts its antiangiogenic effects by targeting VEGF receptor 2 (VEGFR2), VEGFR3, and PDGF receptor beta (PDGFR- β), although a direct effect on tumor cells by targeting the RAF signaling pathway has also been invoked (9, 10). Cediranib is an orally available pan-VEGFR TKI with a biological half-life of 22 hours that facilitates a convenient

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

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doi: 10.1158/1078-0432.CCR-12-3041

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Translational Relevance

The current standard of care in advanced hepatocellular carcinoma (HCC) is sorafenib, an anti-VEGF receptor (VEGFR) tyrosine kinase inhibitor (TKI). The modest efficacy of sorafenib, the recent failures of multiple other TKIs, and the continuing development of other anti-VEGF agents in HCC further emphasized the urgent need for understanding their mechanism of action and identifying biomarkers of efficacy and toxicity. We undertook an exploratory phase II trial of cediranib, a pan-VEGFR TKI, in advanced HCC patients. The results of this translational study show that therapy with cediranib—as seen with other antiangiogenic agents—might benefit only a fraction of HCC patients and that mechanism-based blood biomarkers might potentially be useful in identifying these patients. Translation of this concept in clinical practice will require biomarker-driven randomized trials for patient stratification.

once a day dosing schedule (11). Cediranib is a more potent and selective VEGFR TKI and has a subnanomolar 50% inhibitory concentration for VEGFRs with additional activity against other growth factor receptor kinases but not against RAF (11).

To evaluate whether cediranib is safe and effective in patients with advanced HCC, we conducted a phase II study of cediranib to assess its efficacy and safety profiles. In exploratory studies, we also examined the cediranib-induced circulating angiogenic and inflammatory biomarkers and its steady-state pharmacokinetics (PK) in a subset of patients with advanced HCC.

Patients and Methods

Patient population

The trial was approved by the multi-Institutional Review Board at Dana-Farber/Harvard Cancer Center (Boston, Massachusetts), and by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (trial NCT00427973/CTEP-7147). All patients provided written informed consent before study participation. Eligibility criteria included histologically proven, measurable, locally advanced, or metastatic HCC; first line as well as any prior chemotherapeutic and biologic regimens; prior chemoembolization therapy was allowed only if done more than 4 weeks before study entry and measurable disease outside of the chemoembolization field was present; age ≥ 18 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; Cancer of the Liver Italian Program (CLIP) score ≤ 3 ; and adequate bone marrow, renal, and hepatic function (absolute neutrophil count $\geq 1,000/\mu\text{L}$, hemoglobin ≥ 8 g/dL, platelet count $\geq 75,000/\mu\text{L}$; serum creatinine ≤ 2.0 mg/dL; total bilirubin < 3.0 mg/dL, and aspartate aminotransferase and alanine aminotransferase ≤ 7 times upper normal limit). Exclusion criteria included concurrent malignancies; significant medical comorbidities

including active infection, congestive heart failure, myocardial infarction, serious uncontrolled cardiac arrhythmia, and unstable angina; uncontrolled hypertension; active bleeding; proteinuria at baseline (> 1 g/d); pregnancy or lactation; known brain metastases; prolonged QTc (mean QTc > 470 milliseconds for men and > 490 milliseconds for women); impairment of gastrointestinal function or gastrointestinal disease that may alter the absorption of cediranib. This study was designed and approved in 2005 before the FDA approval of sorafenib for HCC.

Study treatment

Eligible patients received cediranib 30-mg orally once every day without interruption until disease progression, unacceptable toxicity, or withdrawal of consent. Four weeks of the study drug were considered to be one cycle of treatment. Patients were instructed to take the drug either 1 hour before or 2 hours after meals. Doses that were not taken for any reason or expelled when vomiting were not retaken. Cediranib was interrupted and supportive management instituted for grade 3 to 4 hematologic or grade 3 nonhematologic toxicities. Patients with grade 3 or 4 toxicities underwent dose reduction to 20-mg daily, if resolution of the toxicity to less than grade 2 occurred within 21 days; otherwise, treatment was discontinued. A dose of 10-mg daily was considered after consultation with NCI for patients who were benefiting from the treatment and were on study ≥ 3 months. Specific dose reduction instruction for hypertension and proteinuria were provided in the protocol.

On-study evaluations included toxicity assessments, measurement of peripheral blood counts and a full chemistry panel weekly during cycle 1 and every other week for cycle 2 and beyond. Serum alpha-fetoprotein (AFP) was measured monthly in the central MGH Lab. Patients were evaluated with computed tomography (CT) or magnetic resonance imaging (MRI) every 8 weeks to evaluate response and progression. Data were evaluated by independent radiologic review using RECIST criteria (12) as well as per modified (m)RECIST criteria (13, 14).

Circulating biomarker analyses

Peripheral blood was obtained from all patients enrolled at the MGH site ($n = 12$) for studies of early changes in circulating proangiogenic and proinflammatory molecules and cells, as previously described (15). Blood samples were collected in EDTA-containing tubes before and after cediranib therapy on days 1 and 14 of cycle 1. Plasma was harvested by centrifugation and stored at -80°C . Circulating VEGF, placental growth factor (PlGF), sVEGFR1, basic fibroblast growth factor (bFGF), interleukin (IL)-6, IL-8, transforming growth factor α ((TNF- α), gamma interferon (IFN- γ) were measured using multiplex ELISA plates from Meso-Scale Discovery. Hepatocyte growth factor (HGF), insulin-like growth factor 1 (IGF-1), sVEGFR2, angiopoietin 2 (Ang-2), sTie2, soluble c-KIT, carbon anhydrase 9 (CAIX), and stromal cell-derived factor-1 α (SDF1 α) were measured using ELISA kits from

R&D Systems. All samples were assayed in duplicate. The number of CD133⁺CD34⁺CD45^{dim} circulating progenitor cells (CPCs) was counted by flow cytometry using a LSR-II cytometer and FACSDiva software (BD). Biomarker levels measured on quantitative scales were log-transformed and changes were calculated as ratios of on-study to baseline values.

Pharmacokinetics studies

Blood samples to characterize the steady-state PK of cediranib were drawn from a peripheral vein shortly before patients received the dose on days 8 and 15 of cycle 1 and at the following times relative to dosing on day 1 of cycle 2: 5 min and 1, 2, 4, 6, 8, and 24 hours, with the last sample collected before taking the next daily dose. The blood (4.5 mL) was collected in tubes containing EDTA anticoagulant and centrifuged (1,500g, 10 minutes) within 30 minutes. The plasma was removed and stored at -20°C until assayed. The concentration of cediranib in plasma samples was determined by high performance liquid chromatography with tandem mass spectrometry at Quintiles Laboratories Ltd. Assay results for predose samples that were actually collected after the daily dose was taken on days 1 and 15 of cycle 1 and days 1 and 2 of cycle 2 were excluded from analysis of the data. The steady-state minimum concentration of drug in plasma (C_{\min}^{ss}) was calculated as the geometric mean of the assay results for all acceptable predose samples obtained from each patient. The steady-state maximum concentration of drug in plasma (C_{\max}^{ss}) for individual patients was the sample with the highest assayed concentration after taking dose 1 in cycle 2. Cediranib plasma concentration–time curves defined for the 24-hour dosing interval in cycle 2 were analyzed by standard non-compartmental methods using WinNonlin Professional 5.0 software (Pharsight Corp.). The log-linear trapezoidal algorithm was used to estimate the area under the cediranib plasma concentration–time curve for the 24-hour dosing interval ($\text{AUC}_{\tau}^{\text{ss}}$). Apparent oral clearance (CL/F) was calculated as the daily dose divided by $\text{AUC}_{\tau}^{\text{ss}}$. Values of the PK parameters are reported as the geometric mean \pm SD.

Endpoints and statistical methods

The primary endpoint of this study was progression-free survival (PFS) rate at 3 months. We applied a 2-stage design, with maximum sample size set at 34 evaluable patients. The study was to be terminated early and considered negative if $\leq 47\%$ out of first 17 patients survived 3 months progression-free. After the second stage, the study would have been considered positive if at least 20 of 34 evaluable patients (59%) had survived progression-free 3 months. This design yielded at least 90% power to detect a true 3-month PFS rate of at least 69%. It yielded at least 0.90 probability of a negative result if the true 3-month PFS rate was no more than 47%, with at least 0.60 probability of early negative stopping. Secondary endpoints included overall response rate, toxicity, and overall survival (OS). The Kaplan–Meier method was used to estimate the distribution of PFS and OS. We considered patients free of disease progression until

evidence of progression was found in a serial CT/MRI evaluation. Changes in biomarker levels, expressed as ratios of on-study to baseline values, were tested using exact paired Wilcoxon test. *P*-values were adjusted for multiple comparisons over time using method of Genovese and colleagues (16). Correlations of PFS and OS with log-transformed biomarker levels were tested using 2-sided Wald test in Cox regression. Correlations of biomarkers with the number of adverse events (AEs) were quantified as Kendall correlation coefficients and tested using Kendall test. Missing measurements were excluded from analysis. The analyses were conducted using R system (R Foundation for Statistical Software) or SAS 9.2 (SAS Institute).

Results

Patient characteristics

The study enrolled the targeted 17 patients for the first stage between June 2009 and January 2010. All patients were evaluable for efficacy and toxicity based upon intent to treat analysis. Baseline characteristics of the patients enrolled are summarized in Table 1. Briefly, there were 15 men (88%) and 2 women (12%), with a median age of 66 years (range, 46–78 years). Median ECOG performance status was 1 (range, 0–2). Fourteen patients (82%) had underlying Child-Pugh A cirrhosis and 9 (53%) had hepatitis B or C infection. All patients had BCLC stage C and 13 (76%) had extrahepatic disease. Fourteen patients (82%) had received prior systemic therapy including 10 (59%) who had received prior sorafenib at least 4 weeks before cediranib treatment. The median serum bilirubin level was 0.6 mg/dL (range, 0.2–2.4 mg/dL) and AFP level was 3001 ng/mL (range, 2.1–1,348,100) at time of study entry.

Toxicity

A total of 77 treatment cycles were administered, with a median of 3 cycles per patient (range: 1–15). Cediranib treatment was tolerated with manageable adverse effects at the 30-mg daily schedule. The most common all grades AEs, that were considered to be at least possibly related to cediranib, included fatigue, transaminase elevations (SGOT and SGPT), hyponatremia, diarrhea, nausea, hyperbilirubinemia, hypertension, myelosuppression, anorexia, and proteinuria (Table 2). Grade 3 toxicities included hypertension (29%), hyponatremia (29%), hyperbilirubinemia (18%), elevated SGOT (12%) and one patient each (6%) in SGPT, fatigue, cardiac ischemia, hematemesis, and proteinuria. Grade 4 pulmonary embolism and hyperbilirubinemia occurred in 1 patient each. One patient with metastatic HCC and underlying coronary artery disease, s/p stent placement on aspirin and plavix, recent pulmonary embolism on lovenox, received cediranib for 4 weeks and tolerated without complications other than stable fatigue. This patient presented with unwitnessed fall with mental status change and was found to have large left subdural hemorrhage and transtentorial herniation leading to death. Despite the uncertainty of causality, the possibility that this event could have been caused by the investigational agent cannot be entirely discounted.

Table 1. Patient characteristics

Characteristic	Value
No. of patients	17
Male/female (%)	15/2 (88/12)
Median age, years (range)	66 (46–78)
ECOG performance status—no. (%)	
0	5 (29)
1	11 (65)
2	1 (6)
CLIP score—no. (%)	
1	6 (35)
2	4 (24)
3	7 (41)
Child-Pugh class—no. (%)	
A	14 (82)
B	3 (18)
BCLC stage	
C (advanced)	17 (100)
Macroscopic vascular invasion—no. (%)	7 (41)
Extrahepatic spread—no. (%)	13 (76)
HCC etiology	
Hepatitis B	4 (24)
Hepatitis C	5 (29)
Alcohol	2 (12)
Hemachromatosis	1 (6)
Unknown	5 (29)
Median baseline laboratory values (range)	
Albumin (mg/dL)	3.9 (2.6–4.4)
AST (U/L)	51 (20–136)
Total Bilirubin (mg/dL)	0.6 (0.2–2.4)
AFP (ng/mL)	3001 (2.1–1,348,100)
Previous therapy—no. (%)	
Surgical resection	5 (29)
Chemoembolization	3 (18)
Radiation therapy	3 (18)
Systemic therapy	14 (82)
Sorafenib	10 (59)
Prior systemic regimens—no. (%)	
0	3 (18)
1	10 (59)
2	4 (24)

Clinical efficacy

The planned analysis of clinical efficacy was done after all 17 patients were treated at the 30-mg daily dosing schedule. With a median follow-up time of 17 months, the median PFS of this cohort was 5.3 months (95% CI, 3.5–9.7 months; Fig. 1A), and the median OS was 11.7 months (95% CI, 7.5–13.6 months; Fig. 1B). The estimated 3-month PFS rate was 77% (95% CI, 60–99%). The best response was stable disease (SD), which was seen in 5 patients (29%; 4 of 5 patients had received sorafenib). Using mRECIST, only 1 patient had unconfirmed partial response on initial posttreatment scan (classified as SD per

Table 2. Safety profile of cediranib (30-mg daily) in advanced HCC patients

Toxicity (N = 17)	Grade 1–4 (%)	Grade 3 (%)	Grade 4 (%)
Fatigue	14 (82)	1 (6)	–
AST-SGOT	12 (71)	2 (12)	–
Hyponatremia	11 (65)	5 (29)	–
Diarrhea	10 (59)	–	–
Nausea	9 (53)	–	–
Alk.Phosphatemia	8 (47)	1 (6)	–
ALT-SGPT	8 (47)	1 (6)	–
Weight loss	8 (47)	–	–
Anorexia	7 (41)	–	–
Hyperbilirubinemia	7 (41)	3 (18)	1 (6)
Hypertension	7 (41)	5 (29)	–
Hypophosphatemia	7 (41)	1 (6)	–
Proteinuria	7 (41)	1 (6)	–
Thrombocytopenia	6 (35)	–	–
Vomiting	6 (35)	–	–
Dehydration	5 (29)	1 (6)	–
Hypocalcemia	5 (29)	–	–
Leukopenia	5 (29)	–	–
Lymphopenia	5 (29)	1	–
Cough	4 (24)	–	–
Anemia	4 (24)	–	–
Hyperkalemia	4 (24)	–	–
Rash/desquamation	4 (24)	–	–
Fever w/o neutropenia	3 (18)	–	–
Hypoglycemia	3 (18)	–	–
Hypothyroidism	3 (18)	1 (6)	–
Confusion	2 (12)	–	–
Creatinine	2 (12)	–	–
Hand-foot skin reaction	2 (12)	–	–
Hypokalemia	2 (12)	–	–
Stomatitis	2 (12)	–	–
Headache	2 (12)	–	–
Taste disturbance	2 (12)	–	–
Dysphonia	2 (12)	–	–
Cardiac ischemia	1 (6)	1 (6)	–
Hematemesis	1 (6)	1 (6)	–
Hypercalcemia	1 (6)	–	–
Epistaxis	1 (6)	–	–
Pulmonary embolism	1 (6)	–	1 (6)

RECIST); all other assessments were consistent with RECIST. Despite reaching the prespecified goal for the first stage of the trial, the study was stopped and did not proceed to the second stage after reviewing the development program of cediranib by AstraZeneca for reasons unrelated to this study.

PK study

The C_{\min}^{ss} of cediranib was estimated for 16 patients and data required to estimate the AUC_{τ}^{ss} was obtained from 12 patients. Mean values of the steady-state PK

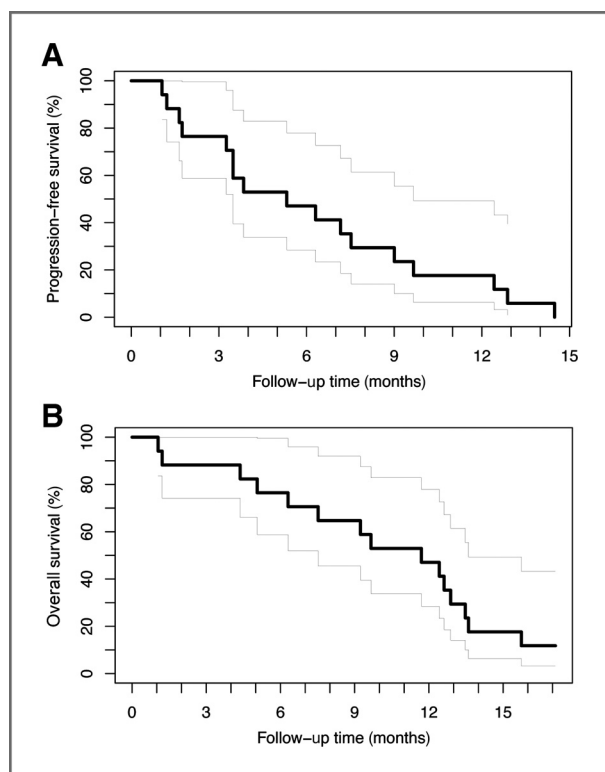


Figure 1. Kaplan-Meier survival distributions. A, PFS and (B) OS with 95% confidence intervals in 17 advanced HCC patients receiving 30-mg cediranib daily. Follow-up time is displayed in months.

parameters for cediranib in these are presented in Table 3 together with comparative data for the same dose and schedule of the drug from a previously reported clinical trial involving solid tumor patients with generally acceptable liver function tests (17). The differences between the mean values of the PK parameters between the 2 populations of patients were not greater than approximately 20%. The potential existence of a correlation between values of the PK parameters and Child-Pugh classification of individual patients could not be assessed because only 3 patients were Child-Pugh B whereas all others were Child-Pugh A.

Exploratory analysis of circulating biomarkers

Increases in plasma PlGF and VEGF were observed as early as day 1 after beginning treatment with cediranib and elevated levels were maintained at day 14 (Table 4). Moreover, cediranib treatment induced a rapid decrease in plasma sVEGFR1 and Ang-2, and a more delayed decrease (at day 14) in sVEGFR2 (Table 4). The levels of inflammatory biomarkers, CAIX and bFGF did not significantly change at these time-points (Supplementary Table S1). However, there was a nonstatistically significant trend for an increase in SDF1 α (day 14) and for decrease in plasma IL-6 and HGF (day 1) and sTie2, TNF- α , and soluble c-KIT (day 14) after cediranib treatment (Supplementary Table S1).

Exploratory correlative analyses showed a significant association of several biomarkers at baseline and on cediranib treatment with PFS, OS, PK parameters, and toxicity in these HCC patients. At baseline, higher plasma levels of sVEGFR1 (HR = 10.68), Ang-2 (HR = 5.32), TNF- α (HR = 31.25), CAIX (HR = 1.63), and higher CPC counts (HR = 10.68) were significantly correlated with a shorter OS after cediranib treatment ($P < 0.05$; Table 5). Moreover, higher baseline plasma levels of VEGF (HR = 2.51), sVEGFR2 (HR = 213.32), and bFGF (HR = 2.06) were significantly correlated with shorter PFS after cediranib treatment ($P < 0.05$; Table 5). For on-treatment biomarkers, OS was directly associated with changes in sVEGFR2 at day 1 (HR = 557.87), whereas PFS was directly associated with changes in bFGF (HR = 3.32) and IGF-1 (HR = 35.17) and inversely associated with changes in IFN- γ (HR = 0.03; $P < 0.05$, all at day 14; Table 5). No significant associations were seen for plasma levels of PlGF, HGF, IL-1 β , IL-6, IL-8, and soluble c-KIT with outcome of cediranib treatment at baseline or on-treatment (data not shown).

The increase in plasma PlGF (at day 1) and the decrease in plasma sVEGFR2 (at day 14) associated directly with AUC $_{\tau}^{ss}$ and C_{min}^{ss} , respectively (Supplementary Table S2).

Finally, the number of AEs after cediranib treatment was inversely correlated with pretreatment concentrations of sVEGFR1, VEGF, and Ang-2 in plasma (Supplementary Table S3). The number of serious AEs (grade 3 and higher) after cediranib treatment was inversely correlated with pretreatment concentration of plasma IFN- γ and number of CPCs (Supplementary Table S3). Cediranib induced an

Table 3. Steady-state pharmacokinetic parameters for cediranib 30-mg once daily po

Parameter (units)	Patients with advanced HCC <i>N</i> = 12-16	Cancer patients with generally acceptable liver function ^a <i>N</i> = 12	Percent difference
C_{min}^{ss} (ng/mL)	22 \pm 21	19 \pm 11	15.8
C_{max}^{ss} (ng/mL)	55 \pm 33	70 \pm 35	-21.4
AUC $_{\tau}^{ss}$ (ng·h/mL)	887 \pm 503	741 \pm 361	19.7

NOTE: Values are reported as the geometric mean \pm SD. Data reported in ref. 17.

Table 4. Early on-treatment changes in plasma biomarkers after daily 30-mg cediranib monotherapy in advanced HCC patients

Biomarker/time-point	Baseline	Day 1	Day 14
PIGF	32.6 [28.7, 42.8] <i>n</i> = 12	86.0 [66.8, 107.0] <i>n</i> = 12	109.9 [73.3, 138.8] <i>n</i> = 11
<i>P</i>	N/A	0.0005	0.0010
<i>P</i> _{adj}	N/A	0.0010	0.0010
VEGF	151 [133, 368]	324 [183, 408]	194 [168, 277]
<i>P</i>	N/A	0.012	0.0049
<i>P</i> _{adj}	N/A	0.012	0.010
sVEGFR1	154 [126, 189]	125 [112, 141]	118 [109, 137]
<i>P</i>	N/A	0.0005	0.024
<i>P</i> _{adj}	N/A	0.0010	0.025
sVEGFR2	5921 [5538, 7454]	6107 [5502, 6817]	4522 [3734, 5024]
<i>P</i>	N/A	0.11	0.0010
<i>P</i> _{adj}	N/A	0.11	0.0020
Ang-2	1012 [621, 2640]	893 [428, 2512]	652 [440, 914]
<i>P</i>	N/A	0.0010	0.054
<i>P</i> _{adj}	N/A	0.0019	0.055

NOTE: *P* values are from exact one-sample Wilcoxon test; *P*_{adj} was calculated after adjustment for multiple comparisons. Data are shown as median concentrations and interquartile ranges in pg/mL in plasma for biomarkers that significantly changed at days 1 and/or 14 during the first cycle of treatment (in bold text).

increase in blood hemoglobin over the first 4 weeks of treatment (Supplementary Table S4), but did not significantly change the WBC, monocyte, lymphocyte, platelet, RBC, or neutrophil counts (not shown).

Discussion

Novel therapies are urgently needed for advanced HCC. With the advent of sorafenib development, there has been renewed hope for systemic antiangiogenic therapies in this setting (17). Sorafenib is an inhibitor of the VEGF pathway, but has clearly a multitargeted TKI activity (9, 10). This CTEP-sponsored phase II study was designed to assess the efficacy and tolerability of a potent and more selective pan-VEGFR TKI—cediranib—in patients with advanced HCC. To gain insight into the role of VEGF inhibition, we also evaluated in exploratory studies the steady-state PK of the TKI agent and circulating angiogenic and inflammatory biomarkers for cediranib treatment in HCC.

When used as monotherapy, cediranib has been often tested using a 45-mg daily schedule and was generally well tolerated (15). However, in a prior study in advanced HCC, the use of cediranib at 45-mg daily led to toxicity in 93% of the patients, including grade 3 or above adverse events including fatigue (46%), anorexia (25%), and hypertension (21%; ref. 18). In our study, we have observed a different tolerability profile with cediranib given at 30-mg daily. Grade 3 events of fatigue and anorexia were low (5% and 0%, respectively). However, as seen with other anti-VEGFR TKIs, we observed a high incidence of grade 3 hypertension (29%), which was manageable with medication. We also observed a high incidence of hyponatremia (65% grades 1–4 including 29% grade 3) and hyperbilirubinemia (41%

grades 1–4 including 18% grade 3 and 6% grade 4). Although most of these patients have received prior systemic treatments, the potential effect of cediranib on worsening underlying cirrhosis should be further explored. In addition, rare bleeding events and pulmonary embolism, known to be associated with antiangiogenic agents, were observed in our study and warrant further evaluation. The safety experience with cediranib dosing in advanced HCC was similar to the cediranib experience in patients with small cell lung cancer (19) as well as with the experience with sunitinib (a broader spectrum TKI) in advanced HCC (20, 21) in that the higher dose schedule was associated with more severe toxicities.

Only modest evidence of antitumor activity (disease stabilization) was found in this small cohort of 17 HCC patients treated with cediranib. The median PFS (5.3 months) and OS (11.7 months) in this group of patients compared favorably to data reported with 45 mg daily dosing of cediranib in advanced HCC (TTP of 2.8 months and OS of 5.8 months; ref. 18). This is likely because of the longer duration of treatment at 30-mg daily dosing. In addition, patient selection bias in different trials because of the heterogeneity of HCC may contribute to the different results. Three-month PFS was calculated in this study with an assumption that patients were free of progression until progression was found in a subsequent CT/MRI scan. This may have introduced a bias in favor of longer PFS, because of delay in ascertainment of the progression occurring between exams. In particular, 4 patients who were found to have a progression during 16-week MRI conducted on study day 99, 106, 106, and 117 were deemed progression-free at 3 months for the purpose of this analysis. Selection of

Table 5. Significant correlations between overall survival (OS) and progression-free survival (PFS) after daily 30-mg cediranib treatment in advanced HCC patients with pretreatment and on-treatment changes (normalized to baseline values) in blood biomarkers (in bold text)

Biomarker/timepoint	Pretreatment Baseline		On-treatment Day 1		Day 14	
	OS	PFS	OS	PFS	OS	PFS
VEGF	1.70 [0.94,3.08], n = 12	2.51 [1.10,5.73], n = 12	2.83 [0.86,9.30], n = 12	0.36 [0.10,1.34], n = 12	1.16 [0.32,4.23], n = 11	1.01 [0.37,2.81], n = 11
P value	0.082	0.029	0.088	0.12	0.82	0.98
sVEGFR1	10.68 [1.65,69.10], n = 12	4.81 [0.99,23.39], n = 12	11.00 [0.62,194.07], n = 12	0.01 [0.00,6.00], n = 12	0.63 [0.15,2.57], n = 11	0.84 [0.23,3.00], n = 11
P value	0.013	0.052	0.10	0.16	0.52	0.79
sVEGFR2	1.18 [0.23,6.04], n = 12	213.32 [6.16,7385], n = 12	10.61 [0.01,10986], n = 12	0.00 [0.00,20.55], n = 12	0.69 [0.10,4.86], n = 11	0.89 [0.04,19.34], n = 11
P value	0.85	0.0030	0.51	0.20	0.71	0.94
Ang-2	5.32 [1.60,17.69], n = 12	1.34 [0.75,2.37], n = 12	2.10 [0.10,46.01], n = 12	0.17 [0.01,2.57], n = 12	1.00 [0.34,2.94], n = 11	0.67 [0.21,2.09], n = 11
P value	0.0064	0.32	0.64	0.20	1.0	0.49
sTie-2	2.14 [0.26,17.47], n = 12	0.07 [0.00,1.52], n = 12	557.87 [5.19,59985.12], n = 12	16.00 [0.14,1800.37], n = 12	0.78 [0.25,2.45], n = 11	1.38 [0.48,3.99], n = 11
P value	0.48	0.090	0.44	0.25	0.67	0.55
bFGF	1.07 [0.74,1.55], n = 12	2.06 [1.20,3.52], n = 12	2.65 [0.90,7.79], n = 12	0.84 [0.32,2.17], n = 12	0.88 [0.51,1.52], n = 11	3.32 [1.20,9.23], n = 11
P value	0.72	0.0088	0.076	0.72	0.65	0.021
IGF-1	0.59 [0.26,1.35], n = 12	1.22 [0.57,2.61], n = 12	9.17 [0.01,14327.88], n = 12	15.88 [0.03,8936.64], n = 12	2.12 [0.40,11.36], n = 11	35.17 [1.99,623.05], n = 11
P value	0.21	0.61	0.55	0.39	0.38	0.015
TNF- α	31.25 [2.99,326.73], n = 12	1.96 [0.36,10.64], n = 12	7.07 [0.14,361.91], n = 12	3.98 [0.06,269.29], n = 12	4.63 [0.68,31.62], n = 11	0.66 [0.16,2.80], n = 11
P value	0.041	0.44	0.33	0.52	0.12	0.57
IFN- γ	0.98 [0.44,2.14], n = 12	0.97 [0.50,1.88], n = 12	1.39 [0.25,7.65], n = 12	1.23 [0.16,9.47], n = 12	0.71 [0.17,2.98], n = 11	0.03 [0.00,0.47], n = 11
P value	0.95	0.93	0.71	0.84	0.64	0.014
CAIX	1.63 [1.02,2.63], n = 12	0.80 [0.51,1.25], n = 12	5.18 [0.37,72.04], n = 12	5.89 [0.51,68.47], n = 12	0.86 [0.34,2.15], n = 11	1.04 [0.47,2.29], n = 11
P value	0.043	0.32	0.22	0.16	0.74	0.92
CD34+CD133+ CPCs	2.61 [1.15,5.92], n = 11	0.94 [0.68,1.30], n = 11	0.94 [0.50,1.75], n = 11	0.73 [0.41,1.30], n = 11	1.64 [0.55,4.88], n = 9	1.87 [0.68,5.18], n = 9
P value	0.022	0.72	0.84	0.28	0.34	0.23

NOTE: P values are from 2-sided Wald test in Cox regression. Data are shown as hazard ratios with 95% confidence intervals.

PFS rate at 3 months as primary endpoint was not based on well-established historic data, as there was a paucity of published data on the natural history of advanced HCC for targeted agents and on the selection of an optimal endpoint when this study was designed (2004–2005). Unfortunately, this study did not proceed into the planned second stage after the sponsor evaluated the overall clinical development program of cediranib in oncology and decided to discontinue this trial. Therefore, the information on clinical efficacy of cediranib was limited because of the small sample size and early stoppage. This study represents the first attempt to evaluate the PK of cediranib in a cohort of patients with underlying Child-Pugh A or B cirrhosis. The mean steady-state PK parameters of cediranib in patients with advanced HCC were largely comparable to values that have been reported for solid tumor patients with generally acceptable liver function tests (17). Despite the small size of this cohort, these findings suggest that degree of hepatic dysfunction presented in the advanced HCC patients evaluated in this study did not have a clinically significant effect on the plasma PK of cediranib.

In spite of the exploratory nature of our biomarker studies, several observations stood out and are consistent with previous data from studies of anti-VEGF agents in HCC and other cancers. Cediranib increased plasma concentrations of PlGF and VEGF, and decreased the concentrations of plasma sVEGFR1 and sVEGFR2 (2 main targets of cediranib) and Ang-2. Although these data are consistent across most studies of anti-VEGF agents (22), future studies should establish if these dynamic biomarkers have PD biomarker value, as suggested by our analysis for PlGF and sVEGFR2.

Moreover, we found significant associations between plasma biomarkers and outcome, which are also consistent with previous results. First, we found an association of high pretreatment VEGF, CAIX (a putative surrogate biomarker of hypoxia), and Ang-2 levels with rapid progression. This indicates that tumor hypoxia and expression of hypoxia-induced factors such as VEGF and Ang-2 may be detectable in circulation and could be a poor prognosis biomarker in HCC—even after anti-VEGF therapy—as previously seen in our HCC studies (1). In addition, circulating levels of the proangiogenic factors bFGF (at baseline and on-treatment) and IGF-1 (on-treatment) correlated with poor outcome. The dual VEGFR/FGFR TKI brivanib alone failed to meet its primary endpoint of improving OS versus placebo in HCC patients who have progressed on sorafenib as well as in the first line setting when compared with sorafenib. Agents targeting IGF-1R are currently being tested in combination with sorafenib in phase I/II trials.

Second, high levels of sVEGFR1 (an active endogenous inhibitor of PlGF and VEGF) and sVEGFR2 were associated with poor survival. Although the significance of sVEGFR2 (a relatively abundant protein in human plasma) remains unknown, the correlation with sVEGFR1 is consistent with our findings in colorectal, brain, and breast cancer patients treated with anti-VEGF agents (23–26). This is supporting the hypothesis that cancer patients with high endogenous

inhibition of VEGF pathway are less likely to respond to anti-VEGF therapies (23). This hypothesis is further supported by the observation that HCC patients with high circulating levels of sVEGFR1—as previously seen in rectal and breast cancer patients treated with anti-VEGF therapy—experienced fewer AEs after cediranib treatment (23, 26).

Third, we found significant correlations between outcome and putative prognostic inflammatory biomarkers: TNF- α concentration and hematopoietic CPC counts at baseline. This is consistent with the potentially critical role of inflammation in HCC response and resistance to anti-VEGF agents (27).

Finally, an increase in circulating IFN- γ was significantly associated with a longer PFS. This suggests the possibility of an antitumor immune response elicited by anti-VEGF therapy. This is consistent with our results using sunitinib in advanced HCC patients, and in line with preclinical evidence (27, 28). Albeit promising, these exploratory results need to be confirmed in larger randomized studies, which should also establish if any of these biomarkers have prognostic or predictive value.

In addition to plasma sVEGFR1, baseline levels of plasma VEGF, Ang-2 and IFN- γ , and CPC number were also inversely associated with AEs. These associations also need to be further validated and their significance remains to be clarified. We also evaluated the changes in weekly standard laboratory blood tests. Similar to sunitinib experience in HCC (27), cediranib induced a mild increase in blood hemoglobin, potentially by relieving the VEGF suppression of erythropoietin production by the liver (29). However, unlike sunitinib, cediranib did not induce bone marrow suppression (27). This could be because of the lower magnitude of off-target effects of cediranib versus sunitinib.

In conclusion, cediranib at 30 mg daily was associated with a high frequency of grade 3 hypertension, hyponatremia, hyperbilirubinemia and showed preliminary evidence of antitumor activity in advanced HCC patients. Exploratory studies further suggested potential PD and response biomarkers of anti-VEGF therapy. Cediranib exhibited similar steady-state PK in HCC patients as in those with other tumor types and normal to near normal hepatic function. Although the clinical development of cediranib has been discontinued because of a corporate-level decision, the hypothesis-generating findings of this study reemphasize that successful development of antiangiogenic therapy in HCC will likely require the use of mechanism-based biomarkers to enrich for the fraction of patients more likely to respond to agents in this class and to identify new targets.

Disclosure of Potential Conflicts of Interest

A.X. Zhu is a consultant/advisory board member of Sanofi-Aventis, Bristol-Myers-Squibb, Eisai, Daiichi Sankyo, and Ecelixis. P. Bhargava is employed by Sanofi Oncology. D.P. Ryan is a consultant/advisory board member of Genomic Health and Boehringer Ingelheim. R.K. Jain has commercial research grants from Dyax, MedImmune, and Roche; ownership interest (including patents) in XTuit, Enlight, and SynDevRx; and is a consultant/advisory board member of Dyax, Noxxon, Enlight, XTuit, H&Q Healthcare Investors, H&Q Life Sciences Investors, and SynDevRx. The other authors disclosed no potential conflicts of interest.

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Acknowledgments

The authors thank Christina Koppel, Olja Pulluqi, and Anna Khachatryan (MGH) for outstanding technical support for biomarker studies.

Grant Support

This study was supported by US National Cancer Center (NCI) Cancer Therapy Evaluation Program (CTEP) and AstraZeneca. The research of R. K. Jain is supported by NCI grants P01-CA80124, R01-CA115767, and R01-CA126642 and Department of Defense Innovator Award W81XWH-10-1-0016. D. G. Duda is supported by NCI grants R21-CA139168 and R01-CA159258 and American Cancer Society grant RSG-11-073-01TBG.

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Received September 24, 2012; revised December 20, 2012; accepted January 21, 2013; published OnlineFirst January 29, 2013.

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