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Phase I/II and Pharmacodynamic Study of Dovitinib (TKI258), an Inhibitor of Fibroblast Growth Factor Receptors and VEGF Receptors, in Patients with Advanced Melanoma

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Abstract

Purpose: Dovitinib (TKI258) is an orally available inhibitor of fibroblast growth factor (FGF), VEGF, and platelet-derived growth factor receptors. This phase I/II dose-escalation study was conducted to evaluate the safety, pharmacodynamics, and preliminary efficacy of dovitinib in the treatment of advanced melanoma.

Experimental Design: Patients with advanced melanoma resistant or refractory to standard therapies or for whom no standard therapy was available were enrolled. Dovitinib was administered at doses ranging from 200 to 500 mg/d.

Results: Forty-seven patients were enrolled. The most frequently reported adverse events were fatigue (77%; grade ≥ 3 , 28%), diarrhea (77%; grade ≥ 3 , 11%), and nausea (77%; grade ≥ 3 , 9%). Six dose-limiting toxicities were observed in the 400-mg and 500-mg dose cohorts, which consisted of grade 3 nausea, fatigue, and diarrhea and grade 4 fatigue events. The maximum tolerated dose was 400 mg/d. The best tumor response was stable disease, which was observed in 12 patients. Increases in plasma FGF23, VEGF, and placental growth factor and decreases in soluble VEGF receptor 2 were noted during the first cycle of treatment, consistent with FGF receptor (FGFR) and VEGF receptor (VEGFR) inhibition. Dynamic contrast-enhanced MRI analysis showed a dose-dependent decrease in tumor blood flow and vascular permeability with dovitinib therapy. A decrease in FGFR phosphorylation was observed in paired tumor biopsy samples from a patient treated with dovitinib at a dose of 400 mg/d.

Conclusions: At a dose of 400 mg/d, dovitinib showed an acceptable safety profile and limited clinical benefit and inhibited FGFR and VEGFR. *Clin Cancer Res*; 17(23); 1–11. ©2011 AACR.

Introduction

Our current understanding of cancer biology has led to the discovery of specific pathophysiologic abnormalities required for the growth and proliferation of cancer cells. These abnormalities have the potential to serve as both biomarkers of disease and targets for therapeutic intervention. These include growth factors, such as VEGF, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and their receptors and downstream signal-

ing components. In melanoma, deregulation of specific growth factors contributes to the development of progression of disease. VEGF signaling is upregulated during melanoma progression and plays a pivotal role in tumor-related angiogenesis (1). Both basic FGF (bFGF) and PDGF signaling have been associated with autocrine stimulation of melanoma growth (1, 2). bFGF and its receptors are expressed in melanoma cells but not in normal melanocytes (1, 2). Inhibition of growth factors, including bFGF, induces tumor cell apoptosis and inhibits the growth of melanoma in preclinical animal models (1). Activation of the FGF pathway also plays an important role in developing an escape mechanism to antiangiogenic drugs targeting VEGF receptors because FGF expression increases with VEGFR-blocking treatment *in vivo* (3). A blockade of the FGF pathway can overcome resistance to VEGFR inhibitors (3).

Dovitinib (TKI258) is a small-molecule inhibitor of FGF receptors (FGFR)1–3, VEGFR1–3, PDGF receptor (PDGFR) β , and other class III receptor tyrosine kinases (4, 5). Inhibition of FGFR1–3 distinguishes dovitinib from other VEGFR inhibitors, such as sorafenib and sunitinib (6). Dovitinib has the potential for antitumor activity through direct inhibition of FGFR and PDGFR, as well as

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Translational Relevance

Therapies targeting molecular pathways of cell proliferation and angiogenesis represent a key advance in cancer treatment in general and melanoma therapy in particular. This study reports the results of a phase I/II study of dovitinib, a tyrosine kinase inhibitor of fibroblast growth factor (FGF) receptors (FGFR), VEGF receptors (VEGFR), and platelet-derived growth factor (PDGF) receptors, in patients with advanced melanoma. The main objectives of this study were safety and efficacy, but a key additional element was the prospective exploratory evaluation of biomarkers to monitor target inhibition. During dovitinib treatment, plasma levels of FGF23, VEGF, and PDGF increased relative to baseline, and plasma levels of soluble VEGFR2 decreased. Phosphorylation of pErk and FGFR3 was reduced in tumor samples. These results indicate that dovitinib inhibited target receptors FGFR and VEGFR and downstream signaling. Monitoring of these biomarkers in future clinical studies may help identify patients who will best respond to dovitinib treatment.

antiangiogenic activity through inhibition of FGFR, VEGFR, and PDGFR (5). Dovitinib inhibits autophosphorylation of its target receptor tyrosine kinases in *in vitro* and *in vivo* tumor models. Tumor regression and stabilization in mouse tumor models was observed at doses of 30 to 100 mg/kg, which is consistent with dose levels required for target modulation (5). The human absorption, distribution, metabolism, and excretion study identified the major metabolites as C-hydroxyl metabolites (in feces) and N-oxide (in plasma) and showed that the majority of the total dose administered was recovered from feces, and less than 21% of the dose was recovered in urine. Dovitinib is metabolized mainly by cytochrome P450 (CYP)1A1/2 and flavin-containing monooxygenase. Flavin-containing monooxygenase is not readily induced or inhibited by any other agents. To a lesser extent, dovitinib could be metabolized by CYP3A4, CYP2C8, and CYP2D6 enzymes.

We conducted a prospective, phase I/II, dose-escalation study to evaluate the maximum tolerated dose (MTD) of dovitinib on a once-daily continuous dosing schedule. Additional endpoints included evaluation of preliminary efficacy, safety, biological activity, and potential biomarkers of angiogenesis to monitor the pharmacodynamic effect of oral dovitinib in advanced melanoma. Functional imaging with dynamic contrast-enhanced MRI (DCE-MRI) was used as a noninvasive *in vivo* assessment of dovitinib efficacy in patients by evaluating tumor blood flow, vascular permeability, and tumor tissue oxygenation before and after dovitinib treatment in patients with metastatic tumors (7, 8). The use of DCE-MRI was designed to provide an early pharmacodynamic assessment of the antiangiogenic effect of dovitinib.

Materials and Methods

This was an open-label, single-arm trial designed with an initial dose-escalation stage followed by a dose-expansion stage. The study was approved by the Institutional Review Board or institutional ethics committee of each participating center and was conducted in accordance with the Declaration of Helsinki. This trial was registered at www.clinicaltrials.gov as NCT00303251. Informed consent was obtained from each patient before participation in the study.

Patient selection

Patients were eligible for the study if they were 18 years or older and had histologically or cytologically documented locally advanced or metastatic melanoma (American Joint Committee on Cancer stage IIIB, IIIC, or IV) that was refractory to or had relapsed after standard therapy or for which no curative standard therapy exists. Patients with at least one measurable or nonmeasurable lesion, as defined by Response Evaluation Criteria in Solid Tumors (RECIST), were eligible for the dose-escalation phase of the study. For the dose-expansion phase, eligible patients had at least one measurable lesion as defined by RECIST. An Eastern Cooperative Oncology Group performance status of 0 or 1 was required for the study. Additional inclusion criteria included the following: absolute neutrophil count $\geq 1,500/\text{mm}^3$, platelet count $\geq 75,000/\text{mm}^3$, hemoglobin ≥ 8.0 g/dL, serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN), bilirubin $\leq 1.5 \times$ ULN, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ ULN, except for subjects with tumor involvement of the liver, who must have had an ALT $\leq 5 \times$ ULN. Patients with impaired cardiac function or clinically significant cardiac disease were not eligible for the study. Patients were excluded if they had received an investigational agent, chemotherapy, targeted therapy, monoclonal antibody therapy, or wide-field radiotherapy within 4 weeks before starting the study drug. Patients were also excluded if they had received biological therapy, received immunotherapy, received limited-field radiation for palliation, undergone major surgery, or received any hematopoietic colony-stimulating factor within 2 weeks before starting the study drug. Patients known to be seropositive for human immunodeficiency virus (screening was not required) or to have a history of another primary malignancy that was clinically significant or required active intervention were also excluded.

Study design

Prior to the start of treatment cycle 1, all patients participated in a 2-day pharmacokinetic (PK) run-in, in which they received a single dose of oral dovitinib on day 1, had blood samples drawn every 2 hours up to 10 hours post-dose, then at 24, 30, and 48 hours postdose. Immediately following the run-in portion of the study, patients received dovitinib once daily in consecutive 28-day cycles with a starting dose of 200 mg/d. Two patients each were enrolled in the 200- and 300-mg/d cohorts, and at least 4 patients

each were assigned to the 400- and 500-mg/d cohorts. Dose escalation was governed by a 2-parameter Bayesian logistic regression model. Evaluable patients for dose-escalation decisions were required to receive a minimum of 22 doses of dovitinib during the first 30 days of the study or have been withdrawn from the study secondary to a dose-limiting toxicity (DLT) before receiving 22 doses of dovitinib. Patients who withdrew from the study without meeting these criteria were replaced within their cohort. At least 6 patients were treated at the MTD.

The primary objectives of the dose-escalation phase were to determine the MTD on the basis of DLTs and to evaluate the PKs of oral dovitinib. The primary objective for the dose-expansion phase was to assess the preliminary efficacy on the basis of RECIST.

Efficacy assessment

Tumor status was evaluated at baseline and every 8 weeks during treatment for all patients by computed tomography scan (conventional or spiral), MRI, or clinical examination. The primary efficacy endpoint was tumor response measured by the rates of clinical response, stable disease, and progressive disease per RECIST. Progression-free survival and overall survival were assessed as secondary efficacy endpoints.

Safety assessment

All patients treated in a cohort were required to undergo safety evaluations on days 8, 15, and 28 of cycle 1 prior to the next dose cohort being enrolled. Afterward, patients underwent a safety evaluation once every cycle. Patients who experienced a DLT had their dose reduced to the next lower dose level. Up to 2 dose reductions were allowed. Inpatient dose escalations were permitted only after 2 patients had been safely treated at the next higher doses. Adverse events (AE) were assigned toxicity grades according to the Common Terminology Criteria for AEs version 3.0.

DLTs, defined in the protocol, included the following: grade ≥ 3 neutropenia for more than 7 consecutive days; grade 3 thrombocytopenia for more than 7 consecutive days; grade 4 thrombocytopenia; febrile neutropenia (absolute neutrophil count, including bands: $<1.0 \times 10^9/L$; fever: body temperature $\geq 38.5^\circ C$); serum creatinine 2 to $3 \times$ ULN for more than 7 consecutive days; grade ≥ 3 serum creatinine; total bilirubin 2 to $3 \times$ ULN for more than 7 consecutive days; grade ≥ 3 total bilirubin; grade 3 AST or ALT for more than 7 consecutive days; grade 4 AST or ALT; grade 4 cardiac hypertension; grade 2 or 3 cardiac hypertension if diastolic blood pressure did not stabilize to within 20 mm Hg (or clinically acceptable range for that patient) of pretreatment measurements, despite concomitant antihypertensive treatment for 7 days or less; grade ≥ 3 cardiac event; grade >1 neurotoxicity event for more than 7 days; any grade 3 event (excluding alkaline phosphatase elevation) that caused an inability to administer dovitinib for more than 7 consecutive days; any grade 4 event (excluding alkaline phosphatase elevation); grade ≥ 3 diarrhea despite the use of optimal antidiarrheal treatments; and any other AE unre-

lated to disease progression, intercurrent illness, or concomitant medications that caused an inability to administer more than 7 doses of dovitinib within a treatment cycle.

Pharmacokinetic evaluation

The terminal half-life of dovitinib was estimated from the 2-day PK run-in. For patients who underwent inpatient dose escalation, samples were collected on day 28 of the first cycle of the new dose, before the dose, and at 2, 4, 6, 8, 10 (optional), and 24 hours after the dose.

Plasma concentrations of dovitinib were measured by liquid chromatography-tandem mass spectrometry. The maximum concentration (C_{max}) and area under the curve from time zero to t (AUC_{0-t}) for dovitinib were estimated on full PK samples collected on days 1, 15, and 28 of cycle 1. Noncompartmental analysis (WinNonLin, V5.2) was conducted to determine key PK parameters, including AUC_{0-t} and half-life.

Pharmacodynamic analysis

Plasma samples were obtained at baseline, on day 15, and on days 26 to 28 to assess the following plasma biomarkers: VEGF, placental growth factor (PLGF), bFGF, soluble VEGFR1 (sVEGFR1), and VEGFR2 (sVEGFR2), FGF23, and c-KIT. The Meso-Scale Discovery platform was used to analyze VEGF, PLGF, bFGF, VEGFR1, and c-KIT levels, and an ELISA (Kinos) was used to analyze FGF23 levels.

Tumor biopsy samples were collected from consenting patients at baseline and within 6 hours of the dosing on day 15 of cycle 1. Tumor cells were stained for pErk with rabbit anti-pErk monoclonal 20G11 (Cell Signaling Technologies), at a concentration of 1 $\mu g/mL$ on a Ventana immunostainer, after antigen retrieval using Ventana CC1 buffer at pH 8 for 30 minutes at $100^\circ C$. Tumor cells were stained for pFGFR3 using custom affinity-purified rabbit anti-phospho FGFR3 (Y724-P) antibody (NVS Emeryville), at a concentration of 1 $\mu g/mL$, after antigen retrieval using Ventana CC1 at room temperature. Ventana OmniMAP was used for detection.

DCE-MRI scans were done in patients with liver metastases of 3 cm or more according to previously reported protocols (7, 9). Assessments were done during baseline and during cycles 1, 2, and 4 for consenting patients. Tumor blood flow, vascular permeability, and tumor tissue oxygenation were quantified as a volume transfer constant (K^{trans}), which is proportional to the degree of tumor perfusion and vascular permeability (8). On the basis of previous research, a decrease in K^{trans} of greater than 20% is considered to be associated with a clinically significant vascular response of the tumor (9). An objective vascular response was defined as the change in K^{trans} and/or in blood-normalized AUC of greater than 2 SD. Levels of FGF23 were assessed as a pharmacodynamic marker of FGFR1 inhibition (10, 11).

Statistical analyses

A 2-stage multinomial design (12) was used for the dose-expansion phase. The primary endpoint was tumor

response. The null hypothesis of H_0 (response rate of $\leq 5\%$ and disease progression rate at month 2 of $\geq 50\%$) was tested against the alternative hypothesis of H_a (response rate of $>5\%$ and disease progression rate at month 2 of $<50\%$). The nominal type I error rate was set at 10%. The dose-expansion phase was powered at 90% for a 15% response rate and a 25% disease progression rate. Twenty patients were needed in the first stage to provide an additional assessment of safety. If the study continued to the second stage, an additional 20 patients would be needed. The safety analysis population comprised all patients who received any amount of study treatment. The safety analyses were done using descriptive statistics.

All biomarker data were \log_2 transformed and subsequently baseline subtracted, to account for the skew that often occurs in these data. This has the effect of modeling the data as the \log_2 change from baseline. Because of their small sample size, the 200- and 300-mg dose cohorts were combined, whereas the 400- and 500-mg cohorts were assessed separately. The changes from baseline were assessed using a 2-way linear mixed-effects model of dose group, time, and their interaction, which accounted for the within-subject correlation using an autoregressive covariance structure and was applied to each biomarker separately. This allowed the model-adjusted mean changes

from baseline and their statistical significance to be computed for each dose group and at the day 15 and day 28 time points, individually. Although the original results were generated in the \log_2 space, this was easily converted to the model-adjusted average ratio from baseline via exponentiation. A false discovery rate (13) adjustment was applied to the P values to control for the multiple statistical tests being done. Spearman correlations were used to determine the degree of association between the imaging pharmacodynamic biomarker K^{trans} and PK biomarker AUC at baseline.

Results

Between April 5, 2006, and September 28, 2008, 47 patients were treated. Of these patients, 27 were enrolled in the dose-escalation segment and 20 were enrolled in stage 1 of the dose-expansion segment. Patient characteristics by treatment are summarized in Table 1.

Clinical efficacy

Preliminary efficacy was a primary objective for the dose-expansion segment only and was evaluated for the full analysis set ($N = 47$). The best overall tumor response after 8 weeks of treatment was stable disease in 12 patients (25.5%) and progressive disease in 25 patients (53.2%);

Table 1. Baseline demographics and patient characteristics

Characteristic	200–300 mg (<i>n</i> = 4)	400 mg (<i>n</i> = 36)	500 mg (<i>n</i> = 7)	Total (<i>N</i> = 47)
Age (y)				
Median	48.5	57.0	62.0	57.0
Range	46–65	26–80	33–71	26–80
Sex, <i>n</i> (%)				
Female	2 (50)	17 (47)	3 (43)	22 (47)
Male	2 (50)	19 (53)	4 (57)	25 (53)
ECOG performance status, <i>n</i> (%)				
0	1 (25)	19 (53)	2 (29)	22 (47)
1	3 (75)	17 (47)	5 (71)	25 (53)
Primary site of cancer, <i>n</i> (%)				
Cutaneous	2 (50.0)	23 (63.9)	4 (57.1)	29 (61.7)
Mucosal	0	2 (5.6)	0	2 (4.3)
Ocular	1 (25.0)	6 (16.7)	1 (14.3)	8 (17.0)
Unknown	1 (25.0)	3 (8.3)	0	4 (8.5)
Other	0	2 (5.6)	2 (28.6)	4 (8.5)
Melanoma subtype, <i>n</i> (%)				
Acral-lentiginous	0	2 (5.6)	0	2 (4.3)
Desmoplastic	0	1 (2.8)	0	1 (2.1)
Mucosal	0	3 (8.3)	1 (14.3)	4 (8.5)
Nodular	1 (25)	4 (11.1)	1 (14.3)	6 (12.8)
Other	1 (25)	0	1 (14.3)	2 (4.3)
Superficial spreading	1 (25)	9 (25.0)	1 (14.3)	11 (23.4)
Unknown	1 (25)	13 (36.1)	3 (42.9)	17 (36.2)
Uveal	0	4 (11.1)	0	4 (8.5)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

the remaining 10 patients were not assessed, or the response was unknown. Stable disease was achieved by 1 of 4 patients at the 200- to 300-mg dose, 10 of 36 patients at the 400-mg dose, and 1 of 7 patients at the 500-mg dose. Seven patients maintained stable disease for at least 4 months (1 of 4 at the 200- to 300-mg dose, 5 of 36 at the 400-mg dose, and 1 of 7 at the 500-mg dose). No patients achieved complete or partial responses. The median progression-free survival from Kaplan–Meier analysis was 2.04 months (95% CI: 1.87–3.68 months), and the median overall survival was 7.49 months (95% CI: 4.30–9.23 months). The study was completed after stage 1 of the dose-expansion phase because the prespecified criteria for continuation were not met.

Safety and tolerability

Drug exposure. The median durations of treatment for the 200- to 300-, 400-, and 500-mg daily dosing groups were 85 (range: 42–279), 58 (range: 1–338), and 62 (range: 27–182) days, respectively. The median duration of treatment for the entire cohort was 58 (range: 1–338) days.

No dose modifications or delays occurred in the 200- to 300-mg dose group. Unplanned dose reductions and/or delays occurred in 13 of 36 (36.1%) patients in the 400-mg group and in 6 of 7 (85.7%) patients in the 500-mg group. The events triggering unplanned dose reductions or interruptions included the following: AEs (15 patients), laboratory abnormalities (3 patients), or medication errors (3 patients); some patients experienced multiple events and dose changes. Dose reductions occurred in 9 patients in the 400-mg group and in 4 patients in the 500-mg group. A total of 24 (51.1%) patients required a dose adjustment or interruption because of an AE of all causes; 19 (40.4%) patients required a dose adjustment or interruption because of a study drug-related AE.

Dose-limiting toxicities. During the dose-escalation phase of the study, no DLTs occurred in the 200- to 300-mg dose cohort ($n = 4$) or in the 400-mg cohort ($n = 6$). As a result, enrollment was opened for the 500-mg/d group. Of the 7 patients treated with 500 mg/d (all evaluable), 3 experienced DLTs: grade 3 fatigue, grade 4 fatigue, and grade 3 diarrhea. The 500-mg/d dose was determined to exceed the MTD. Ten additional patients were then enrolled in the 400-mg/d group, of whom 3 experienced DLTs: grade 3 nausea (1 patient) and grade 3 fatigue (2 patients). Overall, of the 16 patients treated with 400 mg/d in the dose-escalation phase, DLTs were reported in 3 of 10 evaluable patients. The MTD was thus defined as 400 mg/d, and the dose-expansion phase of the study was opened to enroll an additional 20 patients at the 400-mg/d dose.

Adverse events. The AEs occurring in 10% or more of the patients (regardless of the study drug relationship) are summarized in Table 2. The most common AEs observed were diarrhea, fatigue, and nausea (76.6% each, all grades). The most frequent grade 3 and/or grade 4 AEs were fatigue (27.7%), diarrhea (10.6%), upper abdominal pain (8.5%), dehydration (8.5%), and nausea (8.5%). Grade 3 and/or

grade 4 hypertension was reported in 2 patients (4.3%). No hand-foot syndrome was observed. A total of 7 patients discontinued the study because of AEs, including 2 patients enrolled in the dose-escalation phase, for whom the AEs were considered DLTs. Two deaths occurred during the study; both were secondary to the progression of metastatic melanoma, and neither was considered to be related to the study drug.

The percentage of patients with newly occurring or worsening grade 3 or grade 4 abnormal results from the hematologic or clinical chemistry laboratory tests was low overall. The hematology measure associated with the highest overall percentage of patients worsening from baseline to grade 3 was the absolute lymphocyte count, which decreased in 2 of 24 (8.3%) patients. None of the measured hematologic tests worsened from grade 4. Other hematologic measures that worsened from baseline to grade 3 were platelet count and hemoglobin (both of which decreased in 3 of 44 patients, 6.5%) and the white blood cell count (which decreased in 2 of 46 patients, 4.3%). The clinical chemistry tests with the most frequent laboratory abnormalities that worsened from baseline to grade 3 were triglycerides (5 patients, 11.4%) and alkaline phosphatase (6 patients, 13%). Other significant laboratory abnormalities that worsened from baseline to grade 3 included AST (which was elevated in 1 of 46 patients, 2.2%) and ALT (which was elevated in 1 of 46 patients, 2.2%). No patient had a worsening of bilirubin levels to grade 2, 3, or 4. The only abnormality that worsened from baseline to grade 4 was triglycerides, which occurred in 1 patient receiving the 400-mg dose.

Two patients (4.3%) experienced an increase from baseline in the QT interval of more than 60 msec, and no patient experienced a QT prolongation of more than 500 msec. One patient had a QT > 450 msec. No patients had new QTcF increases of more than 60 msec or an absolute QTcF > 500 msec. The ejection fraction decreased from baseline by a mean of 8.3% ($n = 12$), based on multiple gate acquisition scans, and by 1.9% ($n = 16$), based on echocardiograms in evaluable patients. One patient who received the 400-mg dose experienced a grade 2 first-degree atrioventricular block that was reported as a serious AE but was not considered to be related to the study drug according to the investigator.

Pharmacokinetics

Key PK parameters are reported in Supplementary Table S1. Large interindividual variability (CV% ~50%) was observed in the AUC_{0-t} and C_{max} . The mean AUC_{0-t} values in the 200- and 300-mg/d dose cohorts were approximately the same, possibly because of the small sample size (2 patients in each dose cohort) and the large interindividual variability. Dose-dependent increases in AUC_{0-t} or C_{max} were observed in patients receiving 200 to 500 mg/d. At doses of 400 mg/d and lower, AUC_{0-t} on day 15 of cycle 1 was equal to or lower than that on day 1. The half-life of dovitinib was also reduced to approximately 13 hours on day 15 (from 24 hours on day 1), possibly because of autoinduction of CYP1A1/A2 (14). At a dose of

Table 2. AEs occurring in 10% or more of patients, regardless of the study drug relationship

AEs, <i>n</i> (%)	Total (<i>N</i> = 47)		
	All grades	Grade 3	Grade 4
Any	47 (100)	29 (61.7)	6 (12.8)
Diarrhea	36 (76.6)	5 (10.6)	0
Fatigue	36 (76.6)	12 (25.5)	1 (2.1)
Nausea	36 (76.6)	4 (8.5)	0
Vomiting	22 (46.8)	2 (4.3)	0
Weight decrease	17 (36.2)	0	0
Anorexia	16 (34.0)	2 (4.3)	0
Abdominal pain, upper	12 (25.5)	4 (8.5)	0
Dysgeusia	12 (25.5)	0	0
Rash	12 (25.5)	1 (2.1)	0
Dyspnea	11 (23.4)	0	0
Dehydration	10 (21.3)	4 (8.5)	0
Back pain	9 (19.1)	2 (4.3)	0
Dizziness	9 (19.1)	0	0
Dry mouth	8 (17.0)	0	0
Urinary tract infection	8 (17.0)	0	0
Constipation	7 (14.9)	0	0
Dyspepsia	7 (14.9)	0	0
Pyrexia	7 (14.9)	0	0
Cough	6 (12.8)	1 (2.1)	0
Headache	6 (12.8)	0	0
Abdominal pain	5 (10.6)	0	0
Hypertriglyceridemia	5 (10.6)	3 (6.4)	1 (2.1)
Myalgia	5 (10.6)	0	0
Tachycardia	5 (10.6)	0	0

500 mg/d, an accumulation of dovitinib following multiple doses was observed in 2 of 5 patients, suggesting that the accumulation overrode the autoinduction. The mean AUC_{0-t} on day 15 was approximately 2,800 (ng/mL·h) in the 400-mg/d cohort. In the 500-mg/d cohort, the mean AUC_{0-t} on day 15 was approximately 3,400 (ng/mL·h).

Biomarker analysis

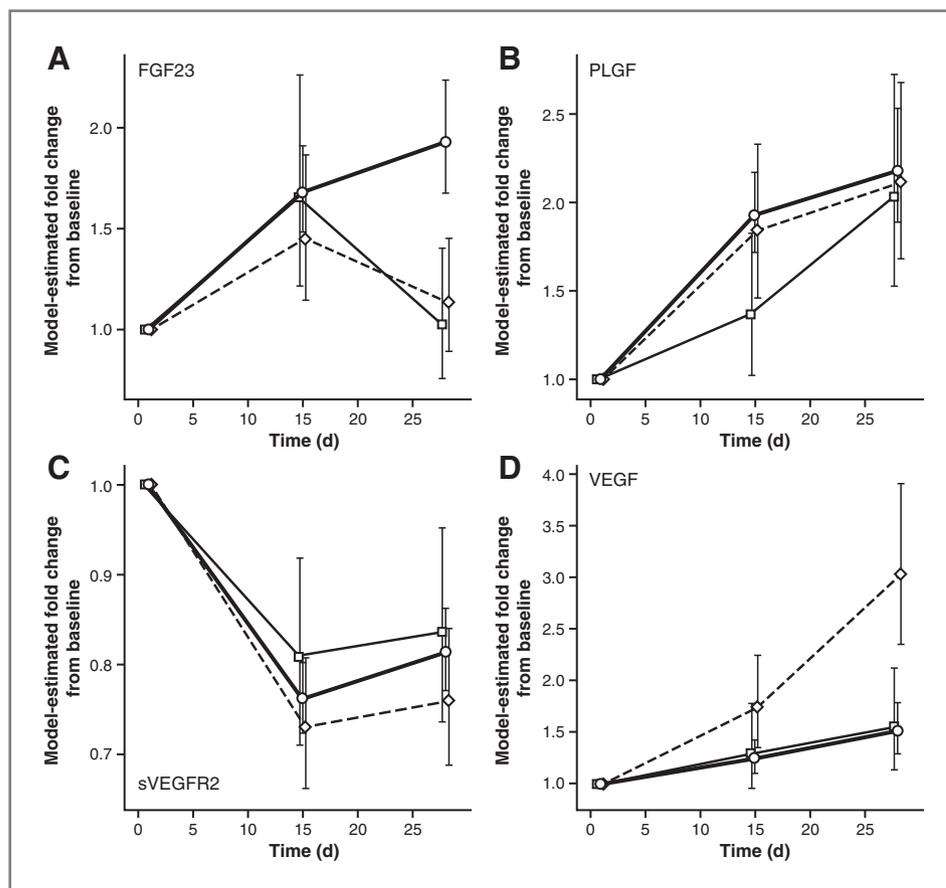
FGFR inhibition by dovitinib was assessed by measuring levels of the ligand FGF23—a circulating factor secreted by osteocytes that plays a critical role in phosphorus homeostasis and vitamin D metabolism (15, 16). FGF23, FGFR1, and coreceptor Klotho complex formation are required for FGF23 signaling to occur (17). Elevation of plasma FGF23 has been shown to be a surrogate pharmacodynamic biomarker of FGFR1 inhibition, probably from compensatory upregulation because of FGFR inhibition (10, 11). Following dovitinib treatment, plasma FGF23 levels increased significantly in all dose cohorts from baseline to day 15 and continued to rise only in the 400-mg/d cohort to day 28 (Fig. 1A).

To confirm FGFR inhibition, pairs of tumor biopsy samples obtained before and after dovitinib treatment (400 mg/d) were examined for levels of phosphorylated FGFR and pErk—a downstream component of FGFR sig-

naling. Collection of tumor biopsies was optional in the protocol for this study, and pre- and posttreatment biopsies were ultimately obtained from only 2 patients. Results from the single biopsy that was of sufficient quality for analysis are presented in Fig. 2. On day 15 of cycle 1, the expression of phosphorylated FGFR3 was lower than at baseline (Fig. 2A). In addition, FGF23 in plasma samples increased initially after dosing on days 1 to 15, then declined from days 15 to 26, but remained above baseline levels (Fig. 2B). Furthermore, in paired tumor biopsy samples, pErk levels on day 15 of cycle 1 were lower than those at baseline (400 mg/d; Fig. 2C). These results indicate that dovitinib therapy inhibits FGFR at the levels of the tumor in patients with melanoma treated with dovitinib 400 mg/d.

Plasma levels of candidate molecules were analyzed as potential biomarkers of angiogenesis. In all dose groups, plasma levels of VEGF on days 15 and 26 in the first cycle were higher than at baseline, suggesting inhibition of VEGFR (Fig. 1D; Table 3). The 200-300-, and 400-mg groups had similar fold increases in VEGF over baseline on day 15 (1.29 and 1.23, respectively), which increased to 1.54- and 1.51-fold, respectively, on days 26 to 28. In the 500-mg dose cohort, VEGF levels increased 1.73-fold on day 15 and 3.03-fold on day 28, which was statistically significant even after correction for the false discovery rate.

Figure 1. Effect of dovitinib on plasma biomarkers: A, FGF23; B, PLGF; C, sVEGFR2; and D, VEGF. Longitudinal plots of the model-estimated fold change from baseline on days 15 and 26 of the first dosing cycle are shown. Thin line, 200 to 300 mg/d dose; bold line, 400 mg/d dose; dashed line, 500 mg/d dose; bars, SE. Mean levels at baseline were as follows: FGF23, 42.34 pg/mL; PLGF, 31.05 pg/mL; sVEGFR2, 172.99 pg/mL; and VEGF, 197.91 pg/mL.



In the 400- and 500-mg dose cohorts, sVEGFR2 decreased significantly from baseline on days 15 and 28 (Fig. 1C). PLGF levels increased from baseline in all dose groups on day 15 and days 26 to 28, with a more than 2-fold increase in each dose cohort on day 28, suggesting inhibition of VEGFR (Fig. 1B; Table 3).

DCE-MRI

A total of 15 patients with liver metastases underwent imaging using DCE-MRI. An objective vascular response (reduction in median K^{trans} of $\geq 20\%$) was seen in none of 3 patients in the 200- and 300-mg cohorts, in 3 of 6 patients in the 400-mg cohort, and in 4 of 6 patients in the 500-mg

Figure 2. Dovitinib inhibits FGFR3 phosphorylation and pErk phosphorylation. A, a pair of tumor biopsy samples stained with anti-pFGFR3 antibody before and after treatment (day 15 of cycle 1, 400 mg/d). B, plasma FGF23 levels from the same patient receiving dovitinib (400 mg/d) on days 1, 15, and 26 of cycle 1 (C1D1, C1D15, and C1D26). C, paired tumor biopsy samples from the same patient stained with anti-pErk antibody before and after treatment (day 15 of cycle 1, 400 mg/d).

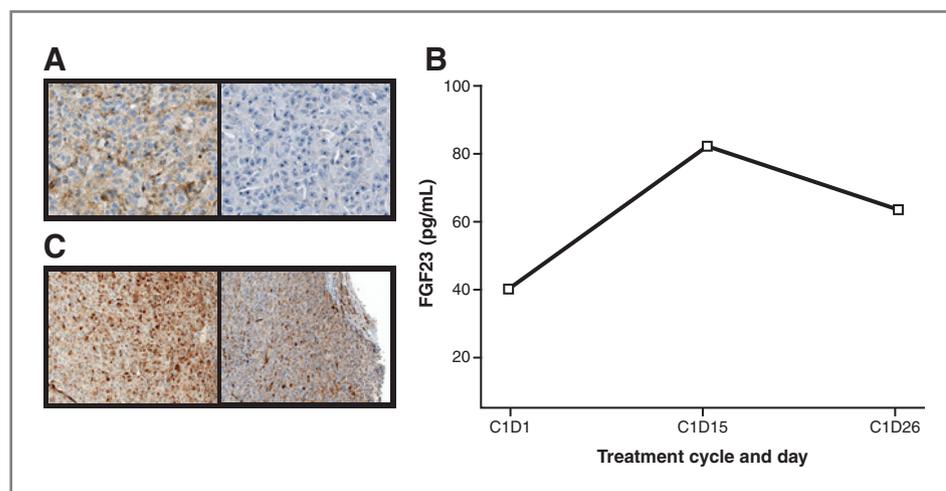


Table 3. Model-adjusted average ratios from baseline observed in plasma levels of biomarkers with false discovery rate-adjusted *P* values for days 15 and 28

Biomarker	Dose group (mg)	Day 15 fold change	Day 15 <i>P</i>	Day 28 fold change	Day 28 <i>P</i>
bFGF	200–300	1.23	0.77	1.34	0.71
	400	0.66	0.15	1.00	1.00
	500	1.83	0.30	2.55	0.10
c-KIT	200–300	1.06	0.74	1.11	0.59
	400	0.94	0.38	0.93	0.38
	500	0.75	0.04	0.88	0.35
FGF23	200–300	1.66	0.23	1.03	0.96
	400	1.68	0.00	1.94	0.00
	500	1.46	0.25	1.13	0.71
PLGF	200–300	1.37	0.41	2.03	0.05
	400	1.93	0.00	2.18	0.00
	500	1.84	0.04	2.12	0.01
sVEGFR1	200–300	0.93	0.89	1.11	0.83
	400	0.67	0.04	0.91	0.70
	500	0.85	0.70	1.19	0.69
sVEGFR2	200–300	0.81	0.22	0.84	0.30
	400	0.76	0.00	0.82	0.00
	500	0.73	0.01	0.76	0.03
VEGF	200–300	1.29	0.59	1.54	0.30
	400	1.23	0.22	1.51	0.04
	500	1.73	0.09	3.03	0.00

cohort. No significant treatment effect was present in the 200- or 300-mg cohorts ($P = 0.58$). However, reductions in median K^{trans} were nearly significant in both the 400-mg ($P = 0.06$) and 500-mg ($P = 0.08$) cohorts. Assessment of the median change in K^{trans} on day 2 of cycle 1 in 15 patients showed that the change in vascularity of the metastatic tumors with dovitinib treatment was dose dependent. In addition, linear regression showed a correlation between a decrease in K^{trans} in liver metastases at an early time point (day 2 of cycle 1) and an increase in plasma dovitinib exposure on day 1 (Fig. 3).

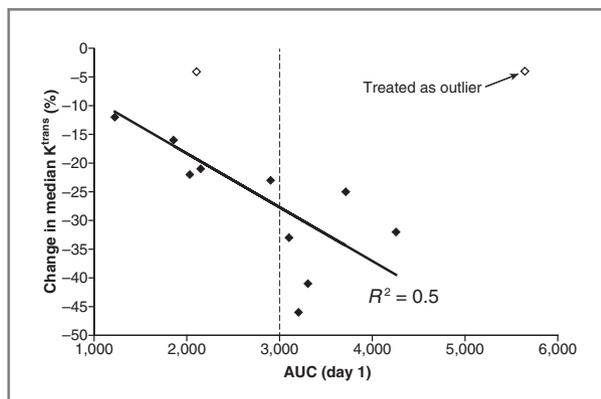


Figure 3. Dovitinib exposure correlates with a change in K^{trans} in liver metastases at an early time point (day 2 of cycle 1) measured by DCE-MRI.

Discussion

This phase I/II study was conducted to determine the MTD, the biological activity, and the preliminary efficacy of dovitinib as a once-daily continuous oral dose in patients with advanced melanoma. Here, the MTD was defined by Bayesian methodology as 400 mg/d. During the dose-escalation phase, DLTs were observed in 3 patients in the 400-mg dose group (grade 3 fatigue in 2 patients and grade 3 nausea in 1 patient) and in 3 patients in the 500-mg dose group (grade 3 and 4 fatigue and grade 3 diarrhea, each in 1 patient), consistent with other agents in this class of drugs. In a previous phase I study of dovitinib in solid tumors that assessed a once-daily continuous dosing schedule, the MTD was defined as 125 mg/d (18). DLTs in that study were as follows: grade 3 hypertension in 1 patient at a continuous dose of 100 mg/d, grade 3 anorexia in a second patient at 175 mg/d, and grade 3 alkaline phosphatase elevation in a third patient at 175 mg/d. In that study, definitions for DLTs were more limited compared with those in the current study. The definitions for DLTs in this study were broad, including any grade 4 event and any grade 3 event causing an inability to administer dovitinib for 7 consecutive days. In this study, the most frequently reported AEs were diarrhea, nausea, and fatigue, all of which occurred across dose levels and were generally mild (grade 1 or 2). These AEs are known side effects of other targeted multikinase inhibitors (19, 20). Hand-foot syndrome is a commonly observed AE in patients receiving small-molecule multikinase inhibitors

(21, 22); notably, no incidents of hand-foot syndrome were observed in this study with dovitinib treatment.

Complete or partial responses were not observed in this study, but 25.5% and 14.9% of the patients achieved stable disease lasting at least 2 and 4 months, respectively. Similar to other antiangiogenic therapies evaluated for the treatment of melanoma (23–27), single-agent dovitinib was not sufficient to meaningfully reduce the tumor burden and provided limited clinical benefit. In a phase II study of axitinib, a VEGFR inhibitor, patients with metastatic melanoma had an objective response rate of 15.6% (28). A phase II study of E7080, another oral multikinase inhibitor with activity against FGFRs, is ongoing (ClinicalTrials.gov, identifier NCT01136967). Thus, therapies targeting VEGFR and FGFR may have clinical utility in the treatment of melanoma. It is increasingly dubious that any single agent will be sufficient to treat this aggressive malignancy, and studies of dovitinib and other multikinase inhibitors as combination therapies may prove more successful.

PK results showed a dose-dependent increase in AUC_{0-t} and C_{max} when dovitinib was administered at doses from 200 to 500 mg/d. Time-dependent PKs of dovitinib were observed, consistent with the findings of other studies (14). Following a continuous daily dose of <400 mg/d, the autoinduction of CYP1A1/A2 resulted in a lower plasma exposure of dovitinib than that on day 1 of cycle 1. However, when the daily dose was increased from 400 to 500 mg, plasma dovitinib concentrations were similar to or greater than those on day 1 of cycle 1, rather than lower, as described above for the lower dose groups. This finding suggests a more pronounced accumulation of dovitinib at higher doses. At the MTD (400 mg/d), no accumulation in exposure was observed, and steady state was achieved on day 15. An additional phase I/II study is ongoing to assess a 5-days-on/2-days-off schedule to decrease the accumulation effect. Preliminary data suggest that this dose schedule is feasible to control drug accumulation and achieve target inhibition and a biological effect (10, 29).

Previous studies have shown that the reduction in tumor vascularity upon exposure to tyrosine kinase inhibitors is significantly correlated with improved clinical outcome in patients with advanced disease (30). Levels of soluble sVEGFR2 and VEGF were inversely correlated in patients with acute lymphoblastic leukemia and a number of other conditions (31–33); similar effects have been observed with the preclinical clinical use of VEGF-targeting drugs (34–37). This observation has stimulated the investigation of these plasma proteins as possible surrogate biomarkers for targeted inhibition of angiogenesis. Dovitinib therapy was associated with an increase in VEGF and PLGF levels and a decrease in sVEGFR2 levels; these changes are indicative of antiangiogenic action associated with inhibition of VEGFR, and VEGF, PLGF, and sVEGFR2 may be useful as potential biomarkers for dovitinib treatment. DCE-MRI analysis showed a dose-dependent change in metastatic tumor vascularity with dovitinib treatment. Furthermore, a higher exposure to dovitinib was associated with a greater reduction in the vascularity of liver metastases at an early time

point (day 2 of cycle 1). These data clearly showed a classic vascular response comparable with that of other anti-VEGF treatments (7, 9).

In addition, treatment with dovitinib led to an increase in plasma FGF23 levels and to an inhibition of downstream targets of FGFR activation (e.g., pErk) in tumor lesions, showing dovitinib inhibition of FGFR signaling in these patients. These results indicate that the panel of circulating proteins examined in this study may have utility as pharmacodynamic biomarkers not only in dovitinib-treated patients with melanoma but also in other cancer types. Taken together, dovitinib treatment resulted in an increase from baseline in FGF23, VEGF, and PLGF and a decrease in sVEGFR2 levels, indicating that dovitinib is capable of inhibiting VEGFR in melanoma cells and suggesting the utility of VEGF, sVEGFR2, and PLGF as pharmacodynamic biomarkers of dovitinib activity.

This study showed that oral dovitinib has an acceptable safety profile and provides pharmacologic inhibition of both the VEGFR and FGFR pathways at the MTD of 400 mg once daily. Future studies are ongoing with a once-daily 5-days-on/2-days-off schedule, which was predicted by modeling to eliminate the accumulation effect on exposure that was shown in this study (14). Results from a phase I/II study in patients with renal cell carcinoma have shown that this dosing schedule eliminates the accumulation effect. Because dovitinib is an inhibitor of FGFRs and VEGFRs, in contrast with other tyrosine kinase inhibitors (e.g., sorafenib and sunitinib), it may be beneficial in FGF-activated cancers. These include breast cancers (due to FGFR1 amplification), bladder cancer (due to FGFR3 mutations), multiple myeloma (due to FGFR3 overexpression), and endometrial cancers (due to FGFR2 mutations), for which dysregulation of the FGFR pathway is important in tumor survival (38–46). FGFR inhibition may also have utility in renal and hepatocellular cancers because the upregulation of FGF signaling seems to play a role in resistance to VEGFR inhibitors (47, 48).

Disclosure of Potential Conflicts of Interest

H. Gardner and M.M. Shi have ownership interest in Novartis. J. Chesney is a consultant and is on the advisory board of Novartis.

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References

- Lazar-Molnar E, Hegyesi H, Toth S, Falus A. Autocrine and paracrine regulation by cytokines and growth factors in melanoma. *Cytokine* 2000;12:547-54.
- Meier F, Caroli U, Satyamoorthy K, Schitteck B, Bauer J, Berking C, et al. Fibroblast growth factor-2 but not mel-CAM and/or beta3 integrin promotes progression of melanocytes to melanoma. *Exp Dermatol* 2003;12:296-306.
- Casanovas O, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell* 2005;8:299-309.
- Kim KB, Saro J, Moschos SS, Hwu P, Tarhini AA, Hwu W, et al. A phase I dose finding and biomarker study of TKI258 (dovitinib lactate) in patients with advanced melanoma. *J Clin Oncol* 2008;26:abstr 9026.
- Lee SH, Lopes de Menezes D, Vora J, Harris A, Ye H, Nordahl L, et al. *In vivo* target modulation and biological activity of CHIR-258, a multi-targeted growth factor receptor kinase inhibitor, in colon cancer models. *Clin Cancer Res* 2005;11:3633-41.
- Karaman MW, Herrgard S, Treiber DK, Gallant P, Atteridge CE, Campbell BT, et al. A quantitative analysis of kinase inhibitor selectivity. *Nat Biotechnol* 2008;26:127-32.
- Liu G, Rugo HS, Wilding G, McShane TM, Evelhoch JL, Ng C, et al. Dynamic contrast-enhanced magnetic resonance imaging as a pharmacodynamic measure of response after acute dosing of AG-013736, an oral angiogenesis inhibitor, in patients with advanced solid tumors: Results from a phase I study. *J Clin Oncol* 2005;23:5464-73.
- Galbraith SM, Rustin GJ, Lodge MA, Taylor NJ, Stirling JJ, Jameson M, et al. Effects of 5,6-dimethylxanthone-4-acetic acid on human tumor microcirculation assessed by dynamic contrast-enhanced magnetic resonance imaging. *J Clin Oncol* 2002;20:3826-40.
- Thomas AL, Morgan B, Horsfield MA, Higginson A, Kay A, Lee L, et al. Phase I study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of PTK787/ZK 222584 administered twice daily in patients with advanced cancer. *J Clin Oncol* 2005;23:4162-71.
- Angevin E, Lopez JA, Pande A, Moldovan C, Shi M, Soria JC, et al. TKI258 (dovitinib lactate) in metastatic renal cell carcinoma (mRCC) patients refractory to approved targeted therapies: A phase I/II dose finding and biomarker study. *J Clin Oncol* 2009;27:abstr 3563.
- Shi M, Kim KB, Chesney J, Wang X, Motwani M, Wang J, et al. Effect of TKI258 on plasma biomarkers and pharmacokinetics in patients with advanced melanoma. *J Clin Oncol* 2009;27:abstr 9020.
- Dent S, Zee B, Dancy J, Hanauske A, Wanders J, Eisenhauer E. Application of a new multinomial phase II stopping rule using response and early progression. *J Clin Oncol* 2001;19:785-91.
- Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J Royal Stat Soc, Series B* 1995;57:289-300.
- Wang X, Anak O, Saro J, Cramer J, Shi M, Zhou W, et al. Population PK modeling and simulation to select a dosing schedule in phase II trials for a novel TKI agent with time-dependent and nonlinear PK. Population Approach Group in Europe Annual Meeting 2009:abstr 1583.
- Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J Bone Miner Res* 2004;19:429-35.
- Sitara D, Razzaque MS, Hesse M, Yoganathan S, Taguchi T, Erben RG, et al. Homozygous ablation of fibroblast growth factor-23 results in hyperphosphatemia and impaired skeletogenesis, and reverses hypophosphatemia in pex-deficient mice. *Matrix Biol* 2004;23:421-32.
- Kurosu H, Kuro-O M. The klotho gene family as a regulator of endocrine fibroblast growth factors. *Mol Cell Endocrinol* 2009;299:72-8.
- Sarker D, Molife R, Evans TR, Hardie M, Marriott C, Butzberger-Zimmerli P, et al. A phase I pharmacokinetic and pharmacodynamic study of TKI258, an oral, multitargeted receptor tyrosine kinase inhibitor in patients with advanced solid tumors. *Clin Cancer Res* 2008;14:2075-81.
- Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:3584-90.
- Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol* 2009;27:3312-8.
- Motzer RJ, Figlin RA, Hutson TE, Tomczak P, Bukowski RM, Rixe O, et al. Sunitinib versus interferon-alfa (IFN- α) as first-line treatment of metastatic renal cell carcinoma (mRCC): Updated results and analysis of prognostic factors. *J Clin Oncol* 2007;25:abstr 5024.
- Azad NS, Aragon-Ching JB, Dahut WL, Gutierrez M, Figg WD, Jain L, et al. Hand-foot skin reaction increases with cumulative sorafenib dose and with combination anti-vascular endothelial growth factor therapy. *Clin Cancer Res* 2009;15:1411-6.
- Eisen T, Ahmad T, Flaherty KT, Gore M, Kaye S, Marais R, et al. Sorafenib in advanced melanoma: A phase II randomised discontinuation trial analysis. *Br J Cancer* 2006;95:581-6.
- Hao D, Hammond LA, Eckhardt SG, Patnaik A, Takimoto CH, Schwartz GH, et al. A phase I and pharmacokinetic study of squalamine, an aminosterol angiogenesis inhibitor. *Clin Cancer Res* 2003;9:2465-71.
- Kim KB, Diwan AH, Papadopoulos NE, Bedikian AY, Camacho LH, Hwu P, et al. A randomized phase II study of EMD 121974 in patients (pts) with metastatic melanoma (MM). *J Clin Oncol* 2007;25:abstr 8548.
- Levitt NC, Eskens FA, O'Byrne KJ, Propper DJ, Denis LJ, Owen SJ, et al. Phase I and pharmacological study of the oral matrix metalloproteinase inhibitor, MMI270 (CGS27023A), in patients with advanced solid cancer. *Clin Cancer Res* 2001;7:1912-22.
- Lewis KD, Robinson WA, Millward MJ, Powell A, Price TJ, Thomson DB, et al. A phase II study of the heparanase inhibitor PI-88 in patients with advanced melanoma. *Invest New Drugs* 2008;26:89-94.
- Fruehauf JP, Lutzky J, McDermott DF, Brown CK, Pithavala YK, Bycott PW, et al. Axitinib (AG-013736) in patients with metastatic melanoma: A phase II study. *J Clin Oncol* 2008;26:abstr 9006.
- Angevin E, Grünwald C, Lin C, Ravaud A, Lopez JA, Krut W, et al. A phase I/II study of TKI258 (dovitinib), a FGFR and VEGFR inhibitor, in patients (pts) with advanced or metastatic renal cell cancer (mRCC): Preliminary phase II results. *Ann Oncol* 2010;21:abstr 507P.
- Lee L, Sharma S, Morgan B, Allegrini P, Schnell C, Brueggner J, et al. Biomarkers for assessment of pharmacologic activity for a vascular endothelial growth factor (VEGF) receptor inhibitor, PTK787/ZK 222584 (PTK/ZK): Translation of biological activity in a mouse melanoma metastasis model to phase I studies in patients with advanced colorectal cancer with liver metastases. *Cancer Chemother Pharmacol* 2006;57:761-71.
- Faderl S, Do KA, Johnson MM, Keating M, O'Brien S, Jilani I, et al. Angiogenic factors may have a different prognostic role in adult acute lymphoblastic leukemia. *Blood* 2005;106:4303-7.
- Tseng JJ, Chou MM, Hsieh YT, Wen MC, Ho ES, Hsu SL. Differential expression of vascular endothelial growth factor, placenta growth factor and their receptors in placenta from pregnancies complicated by placenta accreta. *Placenta* 2006;27:70-8.
- Srikiatkachorn A, Ajariyakhajorn C, Endy TP, Kalayanarooj S, Libraty DH, Green S, et al. Virus-induced decline in soluble vascular endothelial growth factor receptor 2 is associated with plasma leakage in dengue hemorrhagic fever. *J Virol* 2007;81:1592-600.
- Ebos JM, Lee CR, Bogdanovic E, Alami J, Van Slyke P, Francia G, et al. Vascular endothelial growth factor-mediated decrease in plasma soluble vascular endothelial growth factor receptor-2 levels as a surrogate biomarker for tumor growth. *Cancer Res* 2008;68:521-9.
- Ebos JM, Lee CR, Christensen JG, Mutsaers AJ, Kerbel RS. Multiple circulating proangiogenic factors induced by sunitinib malate are tumor-independent and correlate with antitumor efficacy. *Proc Natl Acad Sci USA* 2007;104:17069-74.
- Deprimo SE, Bello CL, Smeraglia J, Baum CM, Spinella D, Rini BI, et al. Circulating protein biomarkers of pharmacodynamic activity of sunitinib in patients with metastatic renal cell carcinoma: Modulation of VEGF and VEGF-related proteins. *J Transl Med* 2007;5:32.
- Deprimo SE, Friece C, Huang X, Smeraglia J, Sherman L, Collier M, et al. Effect of treatment with sunitinib malate, a multitargeted tyrosine kinase inhibitor, on circulating plasma levels of VEGF, soluble VEGF

- receptors 2 and 3, and soluble KIT in patients with metastatic breast cancer. *J Clin Oncol* 2006;24:abstr 578.
38. Byron SA, Pollock PM. FGFR2 as a molecular target in endometrial cancer. *Future Oncol* 2009;5:27–32.
39. Emoto N, Isozaki O, Ohmura E, Ito F, Tsushima T, Shizume K, et al. Basic fibroblast growth factor (FGF-2) in renal cell carcinoma, which is indistinguishable from that in normal kidney, is involved in renal cell carcinoma growth. *J Urol* 1994;152:1626–31.
40. Elbauomy Elsheikh S, Green AR, Lambros MB, Turner NC, Grainge MJ, Powe D, et al. FGFR1 amplification in breast carcinomas: A chromogenic in situ hybridisation analysis. *Breast Cancer Res* 2007;9:R23.
41. Knowles MA. Role of FGFR3 in urothelial cell carcinoma: Biomarker and potential therapeutic target. *World J Urol* 2007;25:581–93.
42. Kwabi-Addo B, Ozen M, Ittmann M. The role of fibroblast growth factors and their receptors in prostate cancer. *Endocr Relat Cancer* 2004;11:709–24.
43. Nomura S, Yoshitomi H, Takano S, Shida T, Kobayashi S, Ohtsuka M, et al. FGF10/FGFR2 signal induces cell migration and invasion in pancreatic cancer. *Br J Cancer* 2008;99:305–13.
44. Yamada SM, Yamada S, Hayashi Y, Takahashi H, Teramoto A, Matsumoto K. Fibroblast growth factor receptor (FGFR) 4 correlated with the malignancy of human astrocytomas. *Neurol Res* 2002;24:244–8.
45. Yoshimura N, Sano H, Hashiramoto A, Yamada R, Nakajima H, Kondo M, et al. The expression and localization of fibroblast growth factor-1 (FGF-1) and FGF receptor-1 (FGFR-1) in human breast cancer. *Clin Immunol Immunopathol* 1998;89:28–34.
46. Fischer H, Taylor N, Allerstorfer S, Grusch M, Sonvilla G, Holzmann K, et al. Fibroblast growth factor receptor-mediated signals contribute to the malignant phenotype of non-small cell lung cancer cells: Therapeutic implications and synergism with epidermal growth factor receptor inhibition. *Mol Cancer Ther* 2008;7:3408–19.
47. Allen E, Walters I, Rivera I, Hanahan D. Anti-angiogenic therapy using brivanib, a combined VEGF and FGF pathway inhibitor, in a mouse model of pancreatic neuroendocrine cancer (PNET), results in sustained vascular blockade, without evidence for evasive/acquired resistance in the form of VEGF-independent revascularization, in contrast to other VEGF inhibitors. *Mol Cancer Ther* 2009;8:abstr B16.
48. Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. *Nat Rev Cancer* 2008;8:592–603.