Phase I Study of Dovitinib (TKI258), an Oral FGFR, VEGFR, and PDGFR Inhibitor, in Advanced or Metastatic Renal Cell Carcinoma

Eric Angevin¹, Jose A. Lopez-Martin², Chia-Chi Lin³, Jürgen E. Gschwend⁴, Andrea Harzstark⁵, Daniel Castellano², Jean-Charles Soria¹, Paramita Sen⁶, Julie Chang⁶, Michael Shi⁶, Andrea Kay⁶, and Bernard Escudier¹

¹Institut de cancérologie Gustave Roussy, Villejuif, France
²12 de Octubre University Hospital, Madrid, Spain
³National Taiwan University Hospital, Taipei, Taiwan
⁴Technische Universität München, München, Germany
⁵University of California, San Francisco, San Francisco, California
⁶Novartis Pharmaceuticals Corporation, East Hanover, New Jersey

Running title
Phase I dovitinib in renal cell carcinoma

Keywords
Dovitinib, fibroblast growth factor receptor, vascular endothelial growth factor receptor, platelet-derived growth factor receptor, renal cell carcinoma

Financial support
Supported by Novartis Pharmaceuticals Corporation for clinical studies and medical editorial assistance.

Corresponding author
Eric Angevin, MD, PhD
Phase I unit (SITEP) & Clinical Research Division
Institut de Cancérologie Gustave Roussy
114 rue Edouard Vaillant
94805 Villejuif Cedex
Tel. 33 (0)1 42 11 50 35
E-Mail: eric.angevin@igr.fr

Conflicts of interest
Chia-Chi Lin has participated in advisory boards for Novartis. Paramita Sen, Julie Chang, Michael Shi, and Andrea Kay are employees of Novartis Pharmaceuticals Corporation. Bernard Escudier has received honoraria from Novartis Pharmaceuticals Corporation, Bayer, Pfizer, GlaxoSmithKline, and Aveo Pharmaceuticals, Inc. All other authors report no conflicts of interest.

Word count: 4793  
Figure/Table count: 6 (3 figures, 3 tables)  
Supplemental table count: 2
Statement of Translational Relevance

Advanced or metastatic RCC is commonly treated with inhibitors of the VEGF, PDGF, and mTOR pathways. However, resistance to these therapies may occur via escape mechanisms, including signaling through the FGF pathway. Therefore, inhibition of FGF and VEGF signaling may provide additional benefit compared with inhibition of VEGF signaling alone. Dovitinib showed greater tumor reduction compared with individual VEGF and PDGF pathway inhibitors in a clear cell RCC 786-O mouse xenograft model. The antitumor activity of dovitinib was explored in a phase I study in patients with metastatic RCC who had failed prior VEGF-targeted and mTOR inhibitor therapies. The antitumor activity (partial responses and long-term stable disease) observed in these heavily pretreated patients supports the role of simultaneous targeting of the FGF, VEGF, and PDGF pathways in metastatic RCC as an approach to overcoming potential resistance to prior antiangiogenic therapies.
Abstract

Purpose: Signaling through the fibroblast growth factor (FGF) pathway may account for tumor resistance to antiangiogenic therapies targeting the vascular endothelial growth factor (VEGF) pathway. Here, dovitinib (TKI258), a potent oral inhibitor of FGF receptor, VEGF receptor (VEGFR), and platelet-derived growth factor receptor tyrosine kinases, is studied in a dose-escalation trial.

Experimental Design: Patients with advanced or metastatic renal cell carcinoma (RCC) with predominant clear cell histology were treated with oral dovitinib 500 or 600 mg/day (5-days-on/2-days-off schedule).

Results: Twenty heavily pretreated patients (median 3 prior regimens) were enrolled, with 16, 11, and 12 patients having previously received at least 1: VEGFR inhibitor, mammalian target of rapamycin (mTOR) inhibitor, and immunotherapy, respectively. Fifteen and 5 patients were treated in 500-mg and 600-mg cohorts, respectively. Three patients experienced dose-limiting toxicities: grade 2 bradycardia (500 mg), grade 4 hypertensive crisis (600 mg), and grade 3 asthenia with grade 2 nausea and vomiting (600 mg). The most common adverse events related to dovitinib were nausea (75%), diarrhea (70%), vomiting (70%), and asthenia (50%), the majority of which were mild (grade 1 or 2), with grade 3 events ≤5% (except asthenia, 15%) and only 1 grade 4 event (hypertensive crisis). Two patients achieved a partial response (500 mg), and 12 patients had stable disease, including 2 patients with long-lasting disease stabilizations (>1 year) in 500-mg cohort.
Conclusions: Dovitinib was tolerable and demonstrated antitumor activity at a maximum tolerated dose of 500 mg on a 5-days-on/2-days-off schedule in heavily pretreated RCC patients.
Introduction

Renal cell carcinoma (RCC) is characterized by highly vascularized tumors that are dependent on angiogenic pathways (1). The vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) pathways are key drivers of angiogenesis. These pathways can be activated by the transcription factor hypoxia-inducible factor (HIF), a protein normally degraded by an E3 ubiquitin-ligase complex containing the von Hippel Lindau (VHL) protein, a tumor suppressor commonly inactivated in clear cell RCC. Tyrosine kinase inhibitors (TKIs) of the VEGF and PDGF pathways, such as sorafenib, sunitinib, pazopanib, and axitinib, are given for advanced disease (2-5). The mammalian target of rapamycin (mTOR) is a central regulator of multiple processes in RCC, including angiogenesis, tumor cell proliferation, and protein metabolism, and the mTOR inhibitor everolimus has also shown activity in this patient population (6). Together, VEGF, PDGF, and mTOR inhibitors have demonstrated a median overall survival of up to 29 months in patients with previously untreated metastatic RCC (mRCC; ref. 7, 8).

The majority of patients with mRCC become resistant or are refractory to angiogenesis inhibitors, including the TKIs and the anti-VEGF monoclonal antibody bevacizumab (9, 10). Mechanisms of resistance include enhancement of receptor signaling to overcome target inhibition, upregulation of HIF following tumor VEGF blockade, tumor hypoxia leading to proangiogenic signaling, upregulation of mTOR complex 2 (which also leads to HIF activation), or activation of alternative angiogenic pathways (1, 11). In addition to VEGF and PDGF, the fibroblast growth factor (FGF) pathway has been shown to play an important role in tumor angiogenesis (12, 13). For
example, highly vascularized tumors often contain high levels of FGFs and FGF receptors (FGFRs) after treatment with VEGF pathway inhibitors (14). In addition, dysregulated expression of FGFs or FGFRs has been described in several cancers, including RCC (15). Preclinical studies also show that FGF signaling is a possible mechanism of escape from and resistance to anti-VEGF therapy (16). Therefore, inhibition of FGF and VEGF signaling may provide additional benefit compared with inhibition of VEGF signaling alone (11).

Dovitinib is a potent, oral inhibitor of receptor tyrosine kinases, including FGFR1 (IC$_{50}$ 8 nM), FGFR2 (IC$_{50}$ 40 nM) and FGFR3 (IC$_{50}$ 9 nM), as well as VEGF receptor (VEGFR) 1 to 3, and PDGF receptor (PDGFR) β (IC$_{50}$ < 40 nM; (17) that has shown antitumor and antiangiogenic effects in preclinical models of colon, breast, bladder, pancreatic, and renal cell cancers (18-23). Here we demonstrate antitumor activity in preclinical models of RCC and report on the dose-escalation portion of a phase I/II study (NCT00715182) to identify the maximum tolerated dose (MTD) of dovitinib on a 5-days-on/2-days-off dosing schedule in repeating 28-day cycles (starting dose, 500 mg) in patients with advanced RCC or mRCC refractory to standard therapies. The phase II portion of this study (24) will be reported separately.

Materials and Methods

Preclinical RCC model

In separate, single experiments, female Harlan nude mice were subcutaneously implanted in the right flank with a single tumor (1 × 10$^7$ clear cell RCC 786-O cells or 1 mm$^3$ clear cell RCC Caki-1 tumor fragments). When the mean tumor volumes reached ~150 mm$^3$, mice were treated daily by oral gavage with vehicle or the mouse MTD of
dovitinib (60 mg/kg), sunitinib (53.6 mg/kg), or sorafenib (60 mg/kg). Ten mice were treated per group, except for some Caki-1 groups which had 9 (sorafenib) or 8 (vehicle) mice due to insufficient numbers of mice with Caki-1 tumors within an acceptable size range. The mean tumor volume was determined for each group, and the percent tumor reduction in mean tumor volume of treated vs. control mice was calculated as 100 – [(mean change of tumor volume of treated animals/mean change of tumor volume of control animals) × 100].

Clinical trial design

This report presents data from the phase I, dose-escalation portion of a multicenter, open-label, phase I/II study (NCT00715182). The primary objective of the dose-escalation phase was to determine the MTD of dovitinib based on incidence of dose-limiting toxicity (DLT) in patients with RCC who had progressed despite standard therapy. Decisions regarding dose escalation were made by overall assessment of the clinical, safety, pharmacokinetic, and pharmacodynamic data in conjunction with the recommendations of the Bayesian logistic regression model guided by the escalation with overdose control principle (25). Cohorts could be expanded for further safety and pharmacokinetic assessments. Secondary objectives included evaluations of safety and preliminary antitumor activity of the dose and administration schedule. Exploratory objectives included evaluation of plasma and tumor biomarkers to monitor the pharmacodynamic effect of oral dovitinib inhibiting FGFR and VEGFR in advanced RCC and assessment of resistance to prior antiangiogenesis therapies.

Dovitinib was administered orally at a dose of 500 or 600 mg/day on a 5-days-on/2-days-off schedule in 28-day cycles. This intermittent schedule was selected
following model-based simulations showing that this schedule could control the
exposure level within a predictable range that facilitated dose titration (26). Dose
adjustments were permitted for patients who were unable to tolerate the dose regimen.
Patients continued treatment until disease progression or unacceptable toxicity. The
study protocol was reviewed and approved by each site's institutional review board,
independent ethics committee, or research ethics board. All patients provided written
consent. The trial was conducted in accordance with the ICH Harmonised Tripartite
Guideline for Good Clinical Practice, applicable local regulations, and the ethical
principles in the Declaration of Helsinki.

Patients

Patients with advanced or metastatic RCC with predominant clear cell histology
were eligible for this study. Other eligibility criteria include: age ≥18 years, Eastern
Cooperative Oncology Group performance status ≤1, life expectancy ≥12 weeks,
absolute neutrophil count ≥1.5 × 10^9/L, platelets ≥75 × 10^9/L, hemoglobin ≥80 g/L,
serum creatinine ≤1.5 × upper limit of normal, and bilirubin ≤1.5 × upper limit of normal.
Patients with brain metastases were eligible. Patients with clinically significant cardiac
disease (including New York Heart Association Class III or IV) or impaired cardiac
function were excluded from the trial. Other exclusion criteria included diabetes mellitus
with signs of clinically significant peripheral vascular disease, pancreatitis, liver disease,
chronic liver impairment, major surgery within 28 days, prior pericarditis, clinically
significant pleural effusion within 12 months, and current ascites requiring 2 or more
interventions/month.
Medications with a potential risk of prolonging the QT interval or inducing torsades de pointes had to be discontinued prior to starting study drug. Use of ketoconazole, erythromycin, carbamazepine, phenobarbital, rifampin, phenytoin, or quinidine within 2 weeks prior to baseline was also excluded due to potential drug-drug interactions.

Assessments

Adverse events (AEs) were graded using Common Terminology Criteria for Adverse Events v3.0. A DLT was defined as an AE or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications occurring within cycle 1 (see Supplemental Table 1). Patients must have received $\geq 75\%$ of the total planned dose in the first 28 days, been observed for $\geq 28$ days following the first dose, and completed all safety evaluations or experienced a DLT in cycle 1 in order to be evaluable for MTD. Electrocardiograms (ECGs) were obtained at baseline (6 predose readings on cycle 1 day 1) and throughout the trial. Tumor response was assessed every 8 weeks by Response Evaluation Criteria In Solid Tumors v1.0. Blood samples for pharmacokinetic analysis were collected predose, on days 1, 8, 15, and 26 of cycle 1, and on days 15 and 28 of cycles 2 and 3. Additional samples were obtained 3, 6, 9, and 24 hours postdose on days 1 and 15 of cycle 1 and 6 hours postdose on day 26 of cycle 1. Pharmacokinetic parameters were determined using a noncompartmental method for area under the curve (AUC), maximum concentration ($C_{\text{max}}$), time to maximum concentration ($T_{\text{max}}$), and half-life ($t_{1/2}$).

Pharmacodynamic analysis
Plasma samples were obtained predose on days 1, 15, and 26 of cycle 1 to assess for VEGF, placental growth factor (PIGF), basic FGF (bFGF), soluble VEGFR2 (sVEGFR2), and FGF23. The Human Growth Factor I Kit was used to analyze VEGF, PIGF, bFGF, and sVEGFR2 (Meso Scale Discovery), and the FGF23 enzyme-linked immunosorbent assay kit (Kainos Laboratories, Inc) was used to analyze FGF23 levels. Values below the lower limit of quantification were set to half of the lower limit of quantification value. Fold-change was computed by subtracting log2-transformed cycle 1 day 1 values from cycle 1 days 15 and 26 values and was assessed using a 1-way linear mixed-effects model with time as the main effect and applying a false discovery rate adjustment to the \( P \) values.

Tumor biopsies, if available, were obtained at baseline and within 6 hours of dosing on cycle 1 day 15 or per investigator-determined posttreatment day. Tumor cells were stained for phosphorylated ERK (pERK) using rabbit anti-pErk monoclonal 20G11 and mouse anti-CD31 monoclonal antibody (Cell Signaling Technology; 1 μg/ml) on an immunostainer (Ventana Medical Systems, Inc.) as previously described (27).

**Results**

**Preclinical RCC model**

To determine whether inhibition of the FGF, VEGF, and PDGF pathways could provide additional benefit compared with inhibition of VEGF and PDGF pathways alone, we studied the effect of dovitinib in a mouse model of human clear cell RCC. 786-O cells are deleted for \( VHL \), which leads to surface accumulation and abnormal activation
of FGFR1 (28). Mice with established subcutaneous 786-O tumors were treated with vehicle or the mouse MTD of dovitinib, sorafenib, or sunitinib. The VEGF and PDGF pathway inhibitors sunitinib and sorafenib induced 17% and 62% reductions in mean tumor volume, respectively, compared with vehicle (Fig. 1A). Dovitinib demonstrated dose-dependent antitumor activity, with 91% reduction in mean tumor volume in treated mice compared with vehicle. Dovitinib activity in RCC xenograft models was also tested using Caki-1 tumors, which induce high plasma concentrations of VEGF that correlate with tumor size, thereby offering a good model for testing antiangiogenic agents (29). In the Caki-1 model, sunitinib and sorafenib induced 66% and 16% reductions in mean tumor volume, respectively, compared with vehicle, whereas dovitinib demonstrated 83% reduction in mean tumor volume. Taken together, these data demonstrate that dovitinib has antitumor activity in RCC models and was as at least as effective as 2 clinically approved TKIs at their MTDs.

**Patient demographics and disposition**

A clinical trial of dovitinib was conducted in RCC patients who had progressed despite standard therapy. Twenty patients with a median age of 55.5 years (range, 29–71) were enrolled in phase I of the study between July 3, 2008, and November 9, 2010, and received at least 1 dose of dovitinib at either 500 mg (n = 15) or 600 mg (n = 5). Patients were Caucasian (n = 16; 80.0%) and Asian (n = 3; 15.0%), with 1 patient’s race not specified (n = 1; 5%). Thirteen (65.0%) patients were identified as having clear cell carcinoma and 7 (35.0%) patients had histologies incompletely recorded as renal adenocarcinoma; however, source documentation verified that these were clear cell carcinoma. Patients had advanced or metastatic cancer, with a median of 3.5 metastatic
sites (range, 1–9), most commonly lung, lymph nodes, and bone (Table 1). Patients were heavily pretreated, having received a median of 3 prior regimens (range, 1–6). All patients (100%) had a prior nephrectomy, and most (85.0%) patients had received prior targeted therapy. Specifically, 16 patients received at least 1 prior VEGF pathway inhibitor (sorafenib, sunitinib, or bevacizumab), including 12 patients who received at least 2 prior VEGF inhibitors. Eleven patients received at least 1 prior mTOR pathway inhibitor (everolimus or temsirolimus), and 10 patients received at least 1 prior mTOR and a VEGF pathway inhibitor (including 8 patients who received 2 prior VEGF pathway inhibitors and an mTOR pathway inhibitor). Additionally, 12 (60.0%) patients received prior immunotherapy. Of note, those patients who were previously treated with VEGF pathway inhibitors demonstrated high baseline plasma levels of bFGF (mean, 146 pg/mL; \( n = 20 \); Fig. 2A). Similarly, patients with RCC in the RECORD-1 trial, a phase 3 study of everolimus in patients progressing after treatment with VEGFR inhibitors (30), showed higher baseline levels of plasma bFGF (mean, 135 pg/mL; \( n = 64 \)), but not 2 other RCC clinical trials from VEGFR-inhibitor-naïve patients (mean 56 pg/mL; \( n = 22 \)) or healthy volunteers (mean, 6.10 pg/mL; \( n = 100 \)). The apparent high baseline levels of bFGF from patients who were previously treated with anti-VEGF inhibitors could support the role of FGF pathway activation in tumor escape of VEGF-targeted therapies (14, 16).

The time from initial diagnosis to most recent relapse was <2 years in 3 (15.0%) patients and ≥2 years in 16 (80.0%) patients, with data from 1 (5.0%) patient missing. The time from the most recent relapse to the start of study drug was <3 months in 16
(80.0%) patients. All patients discontinued from the study, 13 (65.0%) due to disease progression and 6 (30.0%) due to AE(s); 1 (5.0%) patient withdrew consent.

**Determination of MTD**

The first 4 patients were enrolled in cohort 1 (500 mg). All patients were evaluable, and 1 DLT (grade 2 sinus bradycardia leading to discontinuation) was reported. The dose for cohort 2 was escalated to 600 mg, and 5 patients were enrolled, with 1 patient not meeting the minimum exposure criteria, leaving 4 patients evaluable for MTD. Two patients in cohort 2 experienced DLTs (grade 4 hypertensive crisis and grade 3 asthenia with grade 2 nausea and vomiting, both leading to discontinuation). On the basis of the Bayesian logistical regression model recommendation and the clinical safety data, a decision was made to treat the patients in cohort 3 ($n = 4$) with a decreased dosage of 500 mg. All patients in cohort 3 were evaluable for MTD, and no DLTs were observed. Extension cohort 4 included an additional 7 patients treated with 500 mg (all evaluable for MTD), and no DLTs were observed. Upon evaluation of all data, the dose of 500 mg/day on a 5-days-on/2-days-off schedule was declared as the MTD.

**Safety**

The median duration of exposure was 99 days (range, 1–838 days) for all patients and 116 days (range, 1–838 days) and 68 days (range, 5–187 days) in the 500- and 600-mg cohorts, respectively. Four of the 20 (20.0%) enrolled patients had their dovitinib dose reduced following an AE (3 patients in the 500-mg cohorts and 1 patient in the 600-mg cohort). Eight (53.3%) patients in the 500-mg cohorts and 1 (20.0%) patient in the 600-mg cohort experienced 1 ($n = 5, 4$ patients in the 500-mg cohorts and
1 patient in the 600-mg cohort) or ≥1 (n = 4, all in the 500-mg cohorts) dose delays or interruptions. The most common reason for dose delay or interruption was AEs [7 (46.7%) patients in the 500-mg cohorts and 1 (20.0%) patient in the 600-mg cohort]. AEs related to study drug that led to dose delay or interruption were the following in 1 patient each: grade 2 nausea, grade 1 aspartate aminotransferase (AST) increase and grade 2 alanine aminotransferase (ALT) increase, grade 2 nausea/vomiting and grade 1 renal insufficiency, grade 2 weight reduction with grade 1 stomatitis, grade 2 diarrhea and grade 3 dysphagia, grade 1 vomiting, grade 1 anemia, and grade 3 skin rash with grade 3 palmar-plantar erythrodysesthesia.

Overall, the most common AEs suspected to be related to dovitinib treatment were nausea, diarrhea, vomiting, and asthenia (Table 2), occurring at 75.0%, 70.0%, 70.0%, and 50.0%, respectively, in all cohorts. The majority of AEs suspected to be related to treatment were mild (grade 1 or 2). The incidences of grade 3 individual gastrointestinal disorders and skin and subcutaneous tissue disorders were all ≤5%, with only grade 3 asthenia occurring at a higher rate (15%). Only 1 grade 4 event occurred; 1 patient in the 600-mg cohort had hypertension (which developed into a serious AE of hypertensive crisis).

Serious AEs suspected to be related to dovitinib treatment were infrequent (n = 3). Two patients with serious AEs, sinus bradycardia (n = 1, a DLT in the 500-mg cohort) and hypertensive crisis with noncardiac chest pain (n = 1, a DLT in the 600-mg cohort) discontinued and their symptoms resolved. The third patient, who experienced pyrexia (600-mg cohort), did not require study drug delay/interruption and later discontinued due to disease progression.
Six (30.0%) patients discontinued due to AEs, 4 (26.7%) in the 500-mg cohorts and 2 (40.0%) in the 600-mg cohort. Five of these discontinuations were considered related to study drug: nausea/vomiting, rash, and sinus bradycardia in the 500-mg cohorts and hypertension/hypertensive crisis and nausea/vomiting/asthenia in the 600-mg cohort.

One patient, a 71-year-old man, died during the study. The death on day 389 from pneumonia occurred 4 days after his last dose of study drug (500 mg) and was not suspected to be related to the study drug.

Shifts to grade 4 hematologic abnormalities were not observed, and shifts to grade 3 were infrequent and observed only in the 500-mg cohorts: decrease in absolute lymphocytes (n = 1), decrease in absolute neutrophils (n = 2), decrease in platelet count (n = 1), and decrease in white blood cells (n = 1). These events did not lead to study drug interruption or delay. Shifts to grade 3/4 biochemistry abnormalities were also infrequent and observed only in the 500-mg cohorts. These were grade 3 albumin decrease, magnesium increase, lipase increase [without pancreatitis symptoms (grade 2 amylase increase not considered an AE by the investigator)], sodium decrease, and glucose increase (n = 1 each), and grade 4 phosphate decrease post baseline with missing grade at baseline (n = 1). Hepatic laboratory abnormalities were generally mild, with no AST, ALT, or bilirubin values above grade 2 postbaseline. Newly occurring grade 1 and grade 2 increases in AST were observed in 55% and 10% of patients, respectively. The rates were identical for increases in ALT. The only liver function test result observed at grade ≥3 was an increase in alkaline phosphatase levels from grade 1 at baseline to grade 3 in 1 patient.
Nineteen patients were evaluated for QT prolongation (1 patient was not on dovitinib long enough to be considered evaluable). Of the QT prolongation events observed, none were reported as AEs. QTcF increase from baseline to >30 ms was observed in 3 (15.8%) patients in the 500-mg cohorts, with 1 of these patients exhibiting an increase >60 ms (from 377 ms predose on day 1 to 439 ms on day 26). QTcF values of 508 and 509 ms were observed in 1 patient predose on days 26 and 43, respectively. Of note, this patient, who had a high QTcF (484 ms) at screening, continued without dose delay/interruption until disease progression on day 54.

Of 19 evaluable patients, 5 (26.3%) patients, all from the 500-mg cohorts, had newly occurring qualitative ECG abnormalities, most frequently rhythm abnormalities (sinus bradycardia or sinus tachycardia). One patient experienced a DLT, with grade 2 sinus bradycardia on the day of the first dose, 24 hours after normal baseline and predose ECGs, and discontinued from the study. Two of these 5 patients had abnormal baseline ECG findings (flat T waves, and conduction abnormalities and ectopies as first-degree AV block).

Overall, no clinically significant changes in left ventricular ejection fraction or congestive heart failure were observed in the study. In the 500-mg cohorts, 11 of 15 patients had both baseline and posttreatment echocardiogram (ECHO) \((n = 8)\) and multigated acquisition (MUGA) scans \((n = 3)\). Both ECHO and MUGA scans indicated a slight (<10% mean value) intrapatient decrease in cardiac ejection fractions (ECHO mean change from baseline, \(-4.6\%\); range, \(-13.3\%\) to \(2.0\%\); MUGA mean change from baseline \(-8.2\%\); range, \(-25.5\%\) to \(2.0\%\)). One patient (500-mg cohorts) had a MUGA scan decrease from baseline of 71% to 45.5% on day 29 with an overall normal cardiac
ejection fraction. Subsequent ECHO scans on day 84 and day 141 also showed a normal left ventricular ejection fraction of 60%, and this patient continued with no dose interruption until day 838. Of the 2 patients in the 600-mg cohort who had both baseline and posttreatment ECHO scans, no changes in cardiac ejection fractions were observed.

**Efficacy**

On the basis of the central radiologist's review, 2 of the 15 (13.3%) patients in the 500-mg cohorts achieved a partial response (PR). Stable disease (SD) was reported in 60.0% of the patients in each cohort (9 and 3 patients in the 500- and 600-mg cohorts, respectively). Disease control lasted for at least 2 months in 11 (73.3%) and 3 (60.0%) patients and at least 4 months in 9 (60.0%) and 2 (40.0%) patients in the 500- and 600-mg cohorts, respectively. Three patients (20.0%) had progressive disease in the 500-mg cohorts, and the remaining 3 patients had unknown or non-assessed response (1 and 2 in the 500- and 600-mg cohorts, respectively).

The best percentage change from baseline in sum of diameters as per central radiological review is shown in Fig. 3; 1 patient did not have a valid tumor assessment since no posttreatment scan was done due to early discontinuation from the study after the patient experienced a DLT. Two patients, both receiving 500 mg, achieved long-lasting disease stabilization (last confirmed SD response on day 447 and 614). SD was the best response achieved in 2 of the 3 patients presenting with brain metastases at baseline (the third patient had progressive disease) per central review.

Overall, per central review, patients treated at the MTD of 500 mg on a 5-days-on/2 days-off schedule had a median progression-free survival (PFS) of 8.1 months. In
these patients, the median overall survival was 13.3 months. In the 600-mg group, 2 patients experienced a DLT and discontinued from the study. The 3 remaining patients in the 600-mg group were dose reduced to 500 mg and had PFS of 1.5, 3.7 and 3.7 months (1 censored due to withdrawal of consent).

Pharmacodynamics

Plasma samples from patients in the 500-mg cohorts were analyzed for VEGF, PIGF, sVEGFR2, and FGF23 levels on days 1 (baseline), 15, and 26 of cycle 1 (Fig. 2B–E). Elevated plasma FGF23 levels, a surrogate biomarker of FGFR1 inhibition (27), showed a statistically significant increase from baseline on day 15 [110% increase; 95% confidence interval (CI), 28%–143%; \( P = 0.0131 \)]. VEGFR inhibition was demonstrated via a statistically significant increase in PIGF levels on day 26 (48% increase; 95% CI, 20%–81%; \( P = 0.0072 \)) and decreases in sVEGFR2 on day 15 (15% decrease; 95% CI, 24%–6%; \( P = 0.0131 \)) and day 26 (12% decrease; 95% CI, 20%–2%; \( P = 0.0475 \)). Although VEGF levels trended upward, they did not reach statistical significance. This may reflect that most of the patients on this trial had received prior anti-VEGF therapies and were less responsive to additional VEGF pathway inhibition.

Two pairs of tumor biopsies were obtained pre- and post-dovitinib treatment (500 mg/day), but only 1 pair was evaluable for immunohistochemical analysis. To confirm inhibition of FGFR and angiogenesis, tumor samples were examined for levels of pERK, a downstream component of FGFR signaling, and CD31 for microvessel density. At day 27 of cycle 4, a noticeable reduction in the expression of pERK and CD31 compared with baseline was observed (Fig. 2F), indicating that dovitinib inhibits FGFR signaling.
and microvessel formation at the level of the tumor in patients with RCC treated with dovitinib 500 mg/day.

**Pharmacokinetics**

Pharmacokinetic parameters were similar between the 2 dose cohorts (Table 3). The maximal concentration was reached in a median of 6 hours in both dose cohorts on cycle 1 day 1. The day 15 geometric mean areas under the plasma concentration–time curve from time 0 to last measurable sampling time for 500 and 600 mg were 30% and 20% lower, respectively, than the day 1 values. Further, $t_{1/2}$ decreased from ~23 hours (geometric mean) on day 1 to ~10 hours on day 15 in the 500-mg cohorts. These data are supportive of an autoinduction of CYP1A1/2 by dovitinib following multiple doses.

**Discussion**

In the study presented here, dovitinib at the MTD of 500 mg on a 5-days-on/2-days-off schedule was generally well tolerated and demonstrated antitumor activity in heavily pretreated patients with mRCC. At this dose, 2 (13.3%) patients achieved PR, and the median PFS and overall survival were 8.1 and 13.3 months, respectively.

Treatments for RCC currently focus on targeted disruption of angiogenesis via the inhibition of VEGF and PDGF pathways (31). In contrast with other kinase inhibitors, dovitinib inhibits not only VEGF1 to 3 and PDGFRβ, but also FGFR1, FGFR3, and FGFR2 (20). Inhibition of these growth factor receptor kinases should provide greater and broader inhibition of the angiogenesis process as well as provide potent antitumor activities. Indeed, the trend toward greater tumor reduction in mice treated with dovitinib
compared with the VEGF and PDGF pathway inhibitors sunitinib and sorafenib (Fig. 1) may be a result of dovitinib’s ability to inhibit the FGF pathway in addition to the VEGF and PDGF pathways. The greater activity of dovitinib compared with sunitinib was also observed in a recently published report in a mouse RCC tumorgraft model (32). The potential role of the FGF pathway is also supported by the greater mean tumor volume reduction observed with sorafenib compared with sunitinib in the 786-O xenograft model. 786-O cells exhibit surface accumulation and abnormal activation of FGFR1 (28), and sorafenib has a lower IC$_{50}$ for FGFR1 than sunitinib (64 vs 437 nM; ref. (33). Furthermore, FGF pathway activation is an escape mechanism for anti-VEGF therapies, and blockade of the FGF pathway can overcome resistance to VEGFR inhibitors (1, 11, 16). The elevated baseline levels of bFGF in patients previously treated with VEGFR inhibitors (Fig. 2A) support this approach. In addition, pharmacodynamic analysis of plasma biomarkers and tumor biopsies demonstrated both VEGFR inhibition (via increased PlGF levels and decreased sVEGFR2 levels) and FGFR inhibition (via induction of FGF23, a biomarker of FGFR1 inhibition; Fig. 2B–D). Coupled with the clinical activity observed, these data further highlight the potential advantages of targeting the FGF pathway in addition to the VEGF and PDGF pathways for the treatment of RCC.

Dovitinib had a tolerable safety profile at the 500-mg dose level on a 5-days-on/2 days-off schedule. The most common AEs were gastrointestinal in nature and were predominantly grade 1 to 2 in severity. Grade 3 gastrointestinal, dermatologic, and cardiac AEs were infrequent (≤5%), as were hematologic and liver function abnormalities, and grade 4 AEs were rare. The safety profile of dovitinib was as
expected for a TKI in this indication and patient population (2-5). Interestingly, dose-limiting hyperphosphatemia, a common AE observed with more specific FGFR inhibitors (unpublished, personal observation), was not reported in this study. Additionally, hypertension, a common class effect of the VEGFR pathway inhibitors, was observed at a lower rate than typically observed for this class, a finding that will require larger studies for verification.

In a previous study, dovitinib on a continuous daily dosing schedule led to a prolonged and overproportional increase in dose and exposure above 400 mg/day (27). A semimechanistic population pharmacokinetic/pharmacodynamic model was created to evaluate alternative schedules and predicted that intermittent dosing could prevent prolonged accumulation (26). The modeling study also demonstrated similar results for 500 mg on a 5-days-on/2-days-off schedule compared with the 400-mg continuous daily dosing identified as the MTD in a prior study (27). For this reason, the intermittent schedule was selected for analysis in this study, and the results demonstrate that it provided comparable but controllable exposure.

The results of this phase I study suggest that dovitinib may offer clinical benefit in patients who have failed prior VEGF-targeted and mTOR inhibitor therapies, a population that is particularly difficult to treat due to the lack of standard therapeutic options following disease progression. In this study 80% and 55% of patients had received at least 1 prior VEGF pathway inhibitor and at least 1 prior mTOR pathway inhibitor, respectively, and 50% of patients received inhibitors of both pathways. These results were further explored in the phase II dose-expansion component of this study (in patients previously treated with VEGF and mTOR inhibitors; ref. (24)). In addition,
dovitinib is currently being investigated in the phase III study (NCT01223027) of dovitinib vs. sorafenib in patients with metastatic RCC following failure on no more than 1 VEGF pathway–targeted therapy and no more than 1 mTOR-targeted therapy.

Acknowledgments

Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation. We thank Peter J. Simon, PhD, for medical editorial assistance with this manuscript.
References


Table 1. Patient demographics and baseline disease characteristics, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Dovitinib 500 mg n = 15</th>
<th>Dovitinib 600 mg n = 5</th>
<th>All patients N = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (range)</td>
<td>55 (29–71)</td>
<td>56 (36–66)</td>
<td>56 (29–71)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (73.3)</td>
<td>5 (100.0)</td>
<td>16 (80.0)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (26.7)</td>
<td>0</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>12 (80.0)</td>
<td>4 (80.0)</td>
<td>16 (80.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (20.0)</td>
<td>0</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Other (not specified)</td>
<td>0</td>
<td>1 (20.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Stage at initial diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II</td>
<td>2 (13.3)</td>
<td>0</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>III</td>
<td>10 (66.7)</td>
<td>1 (20.0)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (20.0)</td>
<td>4 (80.0)</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3 (20.0)</td>
<td>4 (80.0)</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>1</td>
<td>12 (80.0)</td>
<td>1 (20.0)</td>
<td>13 (65.0)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 (26.7)</td>
<td>3 (60.0)</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>Clear cell adenocarcinoma</td>
<td>11 (73.3)</td>
<td>2 (40.0)</td>
<td>13 (65.0)</td>
</tr>
<tr>
<td>Metastatic site of cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>8 (53.3)</td>
<td>2 (40.0)</td>
<td>10 (50.0)</td>
</tr>
<tr>
<td>Brain</td>
<td>2 (13.3)</td>
<td>1 (20.0)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Liver</td>
<td>5 (33.3)</td>
<td>1 (20.0)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Lung</td>
<td>11 (73.3)</td>
<td>5 (100.0)</td>
<td>16 (80.0)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>10 (66.7)</td>
<td>4 (80.0)</td>
<td>14 (70.0)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (40.0)</td>
<td>4 (80.0)</td>
<td>10 (50.0)</td>
</tr>
<tr>
<td>Time from initial diagnosis to start of study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 to &lt;24 months</td>
<td>2 (13.3)</td>
<td>1 (20.0)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>≥24 months</td>
<td>13 (86.7)</td>
<td>4 (80.0)</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Time since most recent relapse to start of study drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>11 (73.3)</td>
<td>5 (20.0)</td>
<td>16 (80.0)</td>
</tr>
<tr>
<td>≥3 months</td>
<td>3 (20.0)</td>
<td>0</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (6.7)</td>
<td>0</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Prior nephrectomy</td>
<td>15 (100.0)</td>
<td>5 (100.0)</td>
<td>20 (100.0)</td>
</tr>
<tr>
<td>Prior medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>3 (20.0)</td>
<td>0</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>10 (66.7)</td>
<td>2 (40.0)</td>
<td>12 (60.0)</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>12 (80.0)</td>
<td>5 (100.0)</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>VEGF inhibitor&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11 (73.3)</td>
<td>5 (100.0)</td>
<td>16 (80.0)</td>
</tr>
<tr>
<td>mTOR inhibitor&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9 (60.0)</td>
<td>2 (40.0)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td>Other (investigational drug)</td>
<td>0</td>
<td>1 (20.0)</td>
<td>1 (5.0)</td>
</tr>
</tbody>
</table>
ECOG, Eastern Cooperative Oncology Group.

aSeven patients' pathologies were incorrectly recorded as renal adenocarcinoma instead of clear cell renal adenocarcinoma.
bIncludes sorafenib, sunitinib, and bevacizumab.
cIncludes everolimus and temsirolimus.
Table 2. Adverse events (≥2 patients in at least 1 cohort) suspected to be study drug related,\textsuperscript{a} n (%)

<table>
<thead>
<tr>
<th></th>
<th>Dovitinib 500 mg</th>
<th></th>
<th>Dovitinib 600 mg</th>
<th></th>
<th>All</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 15</td>
<td></td>
<td>n = 5</td>
<td></td>
<td>N = 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3</td>
<td>Any grade</td>
<td>Grade 3</td>
<td>Any grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (73.3)</td>
<td>0</td>
<td>3 (60.0)</td>
<td>0</td>
<td>14 (70.0)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (66.7)</td>
<td>1 (6.7)</td>
<td>5 (100.0)</td>
<td>0</td>
<td>15 (75.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (66.7)</td>
<td>0</td>
<td>4 (80.0)</td>
<td>0</td>
<td>14 (70.0)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6 (40.0)</td>
<td>2 (13.3)</td>
<td>4 (80.0)</td>
<td>1 (20.0)</td>
<td>10 (50.0)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (40.0)</td>
<td>1 (6.7)</td>
<td>2 (40.0)</td>
<td>0</td>
<td>8 (40.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (26.7)</td>
<td>0</td>
<td>1 (20.0)</td>
<td>1 (20.0)</td>
<td>5 (25.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (20.0)</td>
<td>1 (6.7)</td>
<td>2 (40.0)</td>
<td>0</td>
<td>5 (25.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>3 (20.0)</td>
<td>0</td>
<td>1 (20.0)</td>
<td>0</td>
<td>4 (20.0)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (13.3)</td>
<td>1 (6.7)</td>
<td>0</td>
<td>0</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (13.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (13.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>2 (13.3)</td>
<td>0</td>
<td>1 (20.0)</td>
<td>0</td>
<td>3 (15.0)</td>
<td>0</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2 (13.3)</td>
<td>1 (6.7)</td>
<td>0</td>
<td>0</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>2 (13.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (13.3)</td>
<td>0</td>
<td>2 (40.0)</td>
<td>0</td>
<td>4 (20.0)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>2 (13.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (13.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2 (13.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>2 (13.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (13.3)</td>
<td>1 (6.7)</td>
<td>0</td>
<td>0</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>2 (13.3)</td>
<td>1 (6.7)</td>
<td>0</td>
<td>0</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>2 (13.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a}One grade 4 event suspected to be study drug related was reported (hypertensive crisis; 600-mg cohort).
Table 3. Pharmacokinetics\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Dovitinib 500 mg</th>
<th>Dovitinib 600 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1 day 1</td>
<td>(n = 15)</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>(AUC_{0-\text{last}}, \text{ h}\cdot\text{ng/mL})</td>
<td>5952.4 (1544.6)</td>
<td>5630.9 (1318.0)</td>
</tr>
<tr>
<td>(C_{\text{max}}, \text{ ng/mL})</td>
<td>340.0 (97.2)</td>
<td>329.6 (99.0)</td>
</tr>
<tr>
<td>(T_{\text{max}}, \text{ h})</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Cycle 1 day 15</td>
<td>(n = 11)</td>
<td>(n = 2)</td>
</tr>
<tr>
<td>(AUC_{0-\text{last}}, \text{ h}\cdot\text{ng/mL})</td>
<td>4411.0 (1921.0)</td>
<td>4448.5 (688.1)</td>
</tr>
<tr>
<td>(C_{\text{max}}, \text{ ng/mL})</td>
<td>303.5 (136.7)</td>
<td>313.5 (70.0)</td>
</tr>
<tr>
<td>(T_{\text{max}}, \text{ h})</td>
<td>6.0</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Abbreviation: \(AUC_{0-\text{last}}\), area under the concentration time curve from time 0 to last available time point.

\textsuperscript{a}Values are mean (standard deviation) except for \(T_{\text{max}}\) (median)
Figure 1. Preclinical activity of dovitinib

Mice implanted with (A) 786-O RCC cells or (B) Caki-1 tumors were treated with daily oral vehicle, or the maximum tolerated dose of dovitinib (60 mg/kg), sorafenib (60 mg/kg) or sunitinib (53.6 mg/kg). Ten mice were treated in each group (except vehicle- and sorafenib-treated Caki-1 mice [n = 8 and 9, respectively]. Values represent the mean ± the standard error. Single asterisk represents $P < 0.05$, and double asterisk represents $P < 0.01$; one-way ANOVA and post hoc Dunnett’s multiple comparison test versus vehicle treated on day 25 (786-O) or day 21 (Caki-1). Due to the deaths of two sorafenib-treated Caki-1 mice, this group could not be statistically evaluated.

Figure 2. Pharmacodynamic analysis of dovitinib in renal cell carcinoma

(A) Box plot of basic fibroblast growth factor levels measured from baseline plasma samples. Whiskers denote the minimum and maximum values, boxes denote the first and third quartiles, and circles denote the median. B-E) Patients in the 500-mg cohorts were analyzed for pharmacodynamic activity. The model adjusted average fold-change from baseline of plasma (B) FGF23, (C) PLGF, (D) sVEGFR2, and (E) VEGF in cycle 1 are shown. Error bars represent ± 1 standard error interval. F) Paired biopsy samples (baseline and cycle 4 day 27) were stained for pERK and CD31 by immunohistochemistry.

Figure 3. Best percentage change from baseline, progression-free survival, and overall survival

Waterfall plot of best percentage change from baseline in sum of diameters of measurable lesions per central radiology review. Of the 15 and 5 patients in the 500- and 600-mg cohorts, 14 and 5 patients, respectively, had valid tumor response assessments. Dotted lines represent 20% increase and 30% reduction from baseline. Asterisk indicates the patient with an overall lesion response of progressive disease but a target lesion response of stable disease.
Figure 1A

Mean tumor volume (mm$^3$) ± SEM

- Vehicle
- Sunitinib
- Sorafenib
- Dovitinib

Days postrandomization

Downloaded from clincancerres.aacrjournals.org on June 28, 2017. © 2013 American Association for Cancer Research.
Figure 2A

Baseline plasma bFGF level (pg/mL)

VEGFR only ($n = 6$)

mTOR only ($n = 1$)

VEGFR + mTOR only ($n = 10$)

Others ($n = 3$)
Figure 3A

Best percent change from baseline

-100
-50
0
50
100

500 mg
600 mg

*
Figure 3B

Censoring times
Dovitinib 500 mg (N = 15)
Number of events: 10
Kaplan-Meier median, months (95% CI)
8.1 (1.8–16.5)

At risk
Event

0 5 7 9 10 10 10 0 0

0 5 0 0 0 0 0 0 0

Time (months)
Probability (%)

0 10 20 30 40 50 60 70 80 90 100

0 6 12 18 24 30 36
Figure 3C

Censoring times
Dovitinib 500 mg (N = 15)
Number of events: 12
Kaplan-Meier median, months (95% CI)
13.3 (13.3–19.7)
Carcinoma PDGFR Inhibitor, in Advanced or Metastatic Renal Cell Carcinoma

Eric Angevin, Jose Lopez-Martin, Chia-Chi Lin, et al.

Clin Cancer Res Published OnlineFirst January 21, 2013.

Updated version  Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-12-2885

Supplementary Material Access the most recent supplemental material at: http://clincancerres.aacrjournals.org/content/suppl/2013/01/21/1078-0432.CCR-12-2885.DC1

Author Manuscript Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.