Multicenter, Phase II Study of Axitinib, a Selective Second-Generation Inhibitor of Vascular Endothelial Growth Factor Receptors 1, 2, and 3, in Patients with Metastatic Melanoma

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Abstract

Purpose: This multicenter, open-label, phase II study evaluated the safety and clinical activity of axitinib, a potent and selective second-generation inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, 2, and 3, in patients with metastatic melanoma.

Experimental Design: Thirty-two patients with a maximum of one prior systemic therapy received axitinib at a starting dose of 5 mg twice daily. The primary endpoint was objective response rate.

Results: Objective response rate was 18.8% [95% confidence interval (CI), 7.2–36.4], comprising one complete and five partial responses with a median response duration of 5.9 months (95% CI, 5.0–17.0). Stable disease at 16 weeks was noted in six patients (18.8%), with an overall clinical benefit rate of 37.5%. Six-month progression-free survival rate was 33.9%, 1-year overall survival rate was 28.1%, and median overall survival was 6.6 months (95% CI, 5.2–9.0). The most frequently (>40%) reported nonhematologic, treatment-related adverse events were fatigue, hypertension, hoarseness, and diarrhea. Treatment-related fatal bowel perforation, a known class effect, occurred in one patient. Axitinib selectively decreased plasma concentrations of soluble VEGFR (sVEGFR)-2 and sVEGFR-3 compared with soluble stem cell factor receptor (sKIT). No significant association was noted between plasma levels of axitinib and response. However, post hoc analyses indicated potential relationships between efficacy endpoints and diastolic blood pressure of 90 mm Hg or higher as well as baseline serum lactate dehydrogenase levels.

Conclusions: Axitinib was well tolerated, showed a selective VEGFR-inhibitory profile, and showed single-agent activity in metastatic melanoma. Further evaluations of axitinib, alone and combined with chemotherapy, are ongoing. Clin Cancer Res; 17(23); 7462–9. ©2011 AACR.

Introduction

The National Cancer Institute estimates that 70,230 new cases of melanoma will be diagnosed and 8,790 deaths from the disease will occur in the United States in 2011 (1). While surgery is often curative with early-stage melanoma, metastatic melanoma has a median survival time of only 6 to 9 months (2). Systemic treatment of advanced disease with currently approved therapies is essentially palliative. Chemotherapy typically consists of single-agent dacarbazine or temozolomide, which have objective response rates (ORR) of 8% and 13%, respectively (3, 4). Combination chemotherapy regimens, such as paclitaxel plus carboplatin, yield similar response rates of 11%, with progression-free survival (PFS) of approximately 18 weeks (5). Immunotherapy, including cytokine treatment, chemoimmunotherapy, and adoptive cell therapy using tumor-infiltrating lymphocytes, has shown promise. The T-cell response potentiator ipilimumab has recently been shown to improve overall survival (OS) in patients with previously treated metastatic disease (6) and high-dose interleukin (IL)-2 has produced a durable 6% complete response (CR) rate in patients with a good performance status (7). While biochemotherapy regimens yield significantly higher response rates, this has not translated into a survival advantage, and high-dose IL-2 and biochemotherapy are associated with significant treatment-related toxicity (7–9). Antiangiogenic agents such as sorafenib and bevacizumab, administered as single agents or in combination, have also been used to treat advanced melanoma with varying degrees of success (10–14). Recently,
Axitinib has been reported to improve OS and PFS compared with dacarbazine in patients with previously untreated melanoma with a mutation in the BRAF gene (15). Despite these advances, the development of treatment resistance continues to be a major hurdle in the treatment of melanoma.

Tumor angiogenesis mediated by the VEGF signaling network is strongly implicated in the invasion and metastasis of melanoma (16–19). VEGF signaling is also involved in the formation of vascular like structures consisting of tumor cells that form during disease progression (20). In patients with melanoma, elevated levels of VEGF are associated with poor outcome (21). In addition, preclinical studies have shown that upregulation of VEGF is associated with IL-2 resistance (22) and that simultaneous inhibition of VEGF receptors (VEGFR)–1 and 2, but not the sole inhibition of either receptor, blocked melanoma growth and metastasis (23). The prominent role of tumor lymphangiogenesis in melanoma progression further implicates VEGFR-3 as a potential target for antiangiogenic therapy (24). Taken together, these findings strongly suggest the involvement of VEGF signaling pathways in melanoma and support the hypothesis that VEGF-targeted therapies may provide effective treatment, either alone or in combination with other therapies.

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Axitinib (AG-013736), a potent and selective second-generation inhibitor of VEGFR-1, 2, and 3 (25–27), has been evaluated both as a single agent and in combination with other therapies (28–32). In a preclinical model of A2058 melanoma cells, axitinib treatment delayed tumor growth in a dose-dependent manner (27). In addition, axitinib treatment inhibited the development of spontaneous lymphatic and lung metastases in an orthotopically implanted M24met human melanoma model (27). Axitinib has shown single-agent activity in several malignancies characterized by high levels of angiogenesis, including metastatic renal cell carcinoma and advanced thyroid cancer, with ORRs ranging from 30% to 44% (28, 29). Recently, a phase III study evaluating axitinib in comparison to sorafenib in patients with cytokine- or tyrosine kinase inhibitor–refractory renal cell carcinoma (NCT00678392; AXIS trial) showed an improvement in PFS for patients treated with axitinib (33). We investigated the tolerability and efficacy of axitinib in a multicenter, phase II, single-arm study in patients with metastatic melanoma.

Materials and Methods

Patients

Patients aged 18 years or older with histologically confirmed metastatic melanoma, who had received no more than one prior systemic therapy for metastatic disease, were eligible for enrollment. Other eligibility criteria included measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST), adequate major organ function, Eastern Cooperative Oncology Group performance status of 0 or 1, and informed consent.

Patients were excluded if they met any of the following criteria: previous treatment with antiangiogenic agents; preexisting uncontrolled hypertension, that is, systolic blood pressure above 140 mm Hg and diastolic blood pressure (DBP) above 90 mm Hg; active seizure disorder or evidence of brain metastases; major surgical procedure or radiation therapy within 4 weeks of treatment.

Study design

This study was a multicenter, open-label, phase II trial of the clinical activity, safety, and tolerability of axitinib in patients with metastatic melanoma. The primary endpoint was ORR, defined as the proportion of patients experiencing CRs or partial responses (PR), based on RECIST. Secondary endpoints included safety, PFS, duration of response, and OS. The relationships between clinical response, axitinib pharmacokinetics, and plasma-soluble proteins were also examined.

This study was approved by the Institutional Review Board of each participating center and was carried out in accordance with the International Conference on Harmonization Good Clinical Practice guidelines protocol, as well as applicable local laws and regulatory requirements. Written informed consent was obtained prior to patients entering the study. The study is registered at ClinicalTrials.gov (NCT00094107).

Study treatment

Axitinib (5 mg) was self-administered orally twice a day with doses spaced approximately 12 hours apart in 4-week treatment cycles. Dose escalations of 20% were administered to patients who were not responding to therapy and if no grade ≥II adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events,
version 3.0) were observed for 8 weeks. Treatment was interrupted in patients with adverse events grade ≥II that was not controlled by supportive medication and was resumed at the same dose after resolution to grade I or baseline levels. Treatment was resumed at a 20% lower dose after resolution to grade I or baseline levels for nonhematologic adverse events grade ≥II, grade IV hematologic adverse events, or recurrent subjectively intolerable toxicity. Dose interruptions also occurred because of uncontrolled elevated blood pressure, hemoptysis, or proteinuria. Treatment was continued until disease progression, significant toxicity, or withdrawal of consent. Patients deriving clinical benefit could continue to receive treatment after meeting criteria for study completion.

**Study assessments**

Blood pressure measurements were collected at each clinic visit. Blood pressure monitors were provided to all patients for daily blood pressure monitoring at home. Patients informed the treating physician for further clinical evaluation in the event of systolic blood pressure above 150 mm Hg or dBP above 90 mm Hg; however, only in-clinic blood pressure measurements were collected in the project database for data analyses. Tumors were measured using computed tomography or MRI at baseline and at least every 8 weeks. Blood samples were collected on day 1 (predose) and every 8 weeks thereafter for analysis of soluble proteins.

**Analysis of blood-based soluble proteins**

Proteins were analyzed with ELISA kits (R&D Systems) as previously reported (34). The VEGF-A ELISA assay measured the VEGF-A (165) and VEGF-A (121) isoforms. The extracellular domain of soluble VEGFR-2 (sVEGFR-2), sVEGFR-3, and soluble stem cell factor receptor (sKIT) were each measured via ELISA as well, after calibration against recombinant proteins consisting of the full-length extracellular domains of the respective receptors. Although, the structural details of sVEGFR-2 and sVEGFR-3 remain to be established, plasma-derived sVEGFR-2 has been reported to be heavily glycosylated and to have a molecular weight of approximately 90 kDa (35). All ELISA assays were run under Good Laboratory Practice conditions and performance specifications of each ELISA were validated as per established guidelines.

**Statistical methods**

The study was conducted using a 2-stage Simon Minimax design (36). Because of lower response rates to conventional chemotherapy for this indication, the p0 and p1 were set at 5% and 20%, respectively. The α and β error rates were set at 0.10 and 0.10, respectively. These criteria resulted in a sample size of 18 patients in stage I and additional 14 patients in stage II (based on Power Analysis and Sample Size 2002 software). At least one confirmed response (i.e., PR or CR) was needed in stage I to allow expansion of the trial to stage II.

Safety and efficacy analyses included all patients who received at least one dose of axitinib and had a baseline assessment of disease. Patients who died, progressed, or discontinued treatment before experiencing a CR or PR were classified as nonresponders. In an unplanned analysis of the subset of patients with or without dBP of 90 mm Hg or higher, survival–time comparisons were conducted using a Cox proportional hazards model, with onset of dBP of 90 mm Hg or higher as a time-dependent covariate. This methodology was used to adjust for covariates that change or vary with time during subject follow-up and controlled for the potential bias of patients who live longer or have greater drug exposure, as well as a greater opportunity to develop high blood pressure. An exploratory analysis of the relationship between outcomes and baseline serum lactate dehydrogenase (LDH) normalized to the median of each laboratory normal range was done using Spearman’s correlation coefficient. An analysis for constructing the historical control OS distribution using prognostic variables (performance status, presence of visceral disease, brain metastases, and gender) was done based on an alternative calculation method described by Korn and colleagues (37).

**Results**

**Patient characteristics**

Thirty-two patients were enrolled in the study and received at least one dose of axitinib. Patient baseline characteristics are summarized in Table 1. All patients had stage IV disease from various types of melanoma including superficial spreading, nodular, lentigo maligna, and uveal melanoma (Table 1). Primary sites were cutaneous (n = 18), uveal (n = 3), mucosal (n = 1), and unknown (n = 10). Twenty-one patients (65.6%) had prior surgery; nearly two thirds of patients (n = 20; 62.5%) had received prior systemic treatment for any disease stage and 50% (n = 16) had prior systemic treatment for metastatic disease. Lung, lymph nodes, and liver were the most common metastatic disease sites. Seventeen patients (53.1%) had elevated baseline LDH levels and 25 patients (78.1%) were classified as M1C at baseline.

The median duration of treatment was 3.8 months (range, 0.4–33.8) with 19 patients (59.4%) receiving therapy for 3.7 months or longer. The median daily dose was 9.5 mg/d (range, 1.7–11.6), with one patient undergoing dose escalation to 14 mg/d. Treatment discontinuation occurred in all patients and was because of lack of efficacy (72.0%; including one patient who withdrew because of disease progression), death (15.6%), and nonfatal adverse events (9.4%) and one patient (3.1%) continued study therapy on a separate treatment-access protocol.

**Clinical activity**

The ORR was 18.8% [95% confidence interval (CI), 7.2–36.4], comprising one CR (3.1%) and 5 PRs (15.6%). The maximum percentage change in target lesion size is shown in Fig. 1. One patient with uveal melanoma experienced a PR. Responding tumor sites included lymph nodes (n = 4) and liver and lung (n = 1 each). Six patients (18.8%) had a best response of stable disease at least 16 weeks in duration,
yielding an overall clinical benefit rate (percentage of patients with a best response ≥ stable disease) of 37.5%. An additional 14 patients (43.8%) had progressive disease, 3 patients (9.4%) had stable disease less than 16 weeks, and 3 patients (9.4%) had missing data. The median duration of response was 5.9 months (95% CI, 5.0–17.0; Fig. 2A). Median PFS was 3.9 months (95% CI, 2.3–6.7; Fig. 2B), and median OS was 6.6 months (95% CI, 5.2–9.0). OS ranged from 0.8 to 42.8 months. Six-month PFS rate was 33.9% and 1-year OS rate was 28.1%. One patient discontinued study after 16.2 months and continued therapy with axitinib on a separate treatment-access study for 1 year; however, additional data were not included in primary PFS or OS analysis.

On the basis of recent findings that VEGF plays a role in resting blood pressure and that blockade of VEGF-mediated upregulation of endothelial and neuronal nitric oxide...
synthase by axitinib may lead to hypertension (38), we considered dBP to be a potential pharmacodynamic marker of axitinib action in individual patients. In an unplanned subgroup analysis with a Cox model that used the onset of dBP of 90 mm Hg or higher as a time-dependent covariate, the relative risk of death was lower in patients with at least one dBP measurement of 90 mm Hg or higher than in patients with dBP less than 90 mm Hg (HR, 0.679; P = 0.387). Median OS in patients who experienced dBP of 90 mm Hg or higher during treatment was 10.7 months (95% CI, 5.9 to not estimable; n = 14) compared with 5.8 months in patients with a dBP less than 90 mm Hg (95% CI, 3.6–6.8; n = 18; Fig. 2C). Median PFS in patients who experienced dBP of 90 mm Hg or higher during treatment was 7.0 months (95% CI, 3.7–14.8) compared with 2.8 months in patients with a dBP less than 90 mm Hg (95% CI, 1.8–4.0). ORR for patients who had at least one dBP of 90 mm Hg or higher during treatment was 21.4% (95% CI, 4.7–50.8) compared with 11.1% (95% CI, 1.4–34.7).

In post hoc analyses, baseline serum LDH levels were also found to be significantly associated with efficacy endpoints. In patients with normal baseline LDH levels (n = 15), median OS was 18.6 months (95% CI, 6.5–not estimable) compared with 5.9 months (95% CI, 2.6–7.4) in patients with baseline LDH levels higher than the normal range (n = 17). Similarly, median PFS of 7.3 months (95% CI, 4.0–14.8) in patients with normal LDH levels was longer than 2.2 months (95% CI, 1.8–4.2) in those with elevated LDH levels. ORR was 26.7% for patients with normal LDH level compared with 11.8% for those with elevated LDH level [treatment difference = 14.9% (95% CI, −12.2% to 42.0%)]. Outcomes for patients with higher baseline LDH levels were worse than those for patients with baseline LDH levels within normal limits, which is consistent with other trials evaluating metastatic melanoma. OS based on prognostic variables of performance status, presence of visceral disease, brain metastases, and gender was similar to historical control for this population of 32 patients (data not shown).

Safety
The most frequently (>15%) reported nonhematologic, treatment-related adverse events included fatigue, hypertension, hoarseness, and diarrhea (Table 2). The majority of these events were grade I/II. The most common grade ≥III adverse event was fatigue (n = 7; 21.9%). Hypertension was reported in 14 patients (43.8%), most of which was mild to moderate in severity (grade I/II). Grade III hypertension was reported in 3 patients (9.4%). There were no other grade III adverse events that were considered treatment related. Grade II treatment–related proteinuria was reported in 2 patients (6.3%), on the basis of laboratory data. Two patients (6.3%) experienced grade I/II hemoptysis, of which only one case was assessed as treatment related. No grade III/IV hematologic laboratory abnormalities were observed (Table 2). Grade III clinical chemistry abnormalities were observed in 5 patients and no grade IV findings were reported.

Seven patients (21.9%) had axitinib dose reductions because of adverse events and 22 patients (68.8%) had treatment interruptions because of adverse events, the most common of which were fatigue (n = 6), hypertension (n = 6), arthralgia (n = 3), and hand–foot syndrome (n = 3). Adverse events related to study treatment and resulting in discontinuation were grade IV fatigue, grade I hemoptysis, and grade V bowel perforation (n = 1 each).

Eight patients (25.0%) died because of an adverse event during the active treatment period or within 28 days of their last axitinib dose. Six of these patients (19%) died because of disease progression or disease-related symptoms that were unrelated to study treatment. One patient died because of cerebrovascular accident deemed unrelated to study treatment by the investigator. One death was assessed as treatment-related and occurred in a 56-year-old female who experienced a grade V bowel perforation, although tumor progression could not be excluded as a cause of death.

Modulation of blood-based soluble proteins
Plasma concentrations of sVEGFR-2 and sVEGFR-3 were decreased to the greatest extent after 2 cycles of axitinib therapy (mean ratio to baseline ± SEM: sVEGFR-2: 0.58 ± 0.03, P < 0.0001 and sVEGFR-3: 0.61 ± 0.05, P < 0.0005)

Table 2. Safety findings: treatment-related adverse events reported by at least 15% of patients

<table>
<thead>
<tr>
<th>Nonhematologic adverse events</th>
<th>Number of patients, N = 32, n (%)</th>
<th>Total</th>
<th>Grade III/IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>19 (59.4)</td>
<td>7 (21.9)</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>14 (43.8)</td>
<td>3 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Hoarseness</td>
<td>11 (34.4)</td>
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<td></td>
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<tr>
<td>Diarrhea</td>
<td>10 (31.3)</td>
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<td></td>
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<tr>
<td>Nausea</td>
<td>8 (25.0)</td>
<td>0</td>
<td></td>
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<tr>
<td>Arthralgia</td>
<td>6 (18.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>5 (15.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>5 (15.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pain in limb</td>
<td>5 (15.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5 (15.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (15.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>5 (15.6)</td>
<td>0</td>
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</tr>
<tr>
<td>Weight decreased</td>
<td>5 (15.6)</td>
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<tr>
<td><strong>Hematologic abnormalities</strong></td>
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<tr>
<td>Anemia</td>
<td>7 (21.9)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>5 (15.6)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

*Not otherwise specified.

*On the basis of laboratory data.
Axitinib in Metastatic Melanoma

Figure 3. Mean (±SEM) change from baseline in plasma levels of sVEGFR-2, sVEGFR-3, and soluble stem cell factor receptor (sKIT; n = 7–25). Wilcoxon signed-rank test NS, not significant. *P < 0.002; †P < 0.0001; ‡P < 0.0005.

Discussion

These results show that axitinib has single-agent activity in patients with stage IV melanoma of which 78% were classified as poor prognoses M1C and 53% had elevated baseline serum LDH levels. Antitumor activity was observed with an ORR of 18.8%, including one CR and 5 PRs, with responses persisting for a median duration of 5.9 months. An additional 6 patients (18.8%) experienced stable disease lasting at least 16 weeks. This response rate is comparable to the 8% to 13% ORR provided by standard single-agent dacarbazine or temozolomide, or combination therapy of metastatic melanoma. In this clinical trial, the same pattern of modulation has been reported for other angiogenesis inhibitors (44). Axitinib activity (40). In the current study, patients who experienced DBP of 90 mm Hg or higher (grade I hypertension) during treatment had a longer survival time than those who did not (median OS, 10.7 vs. 5.8 months, respectively). Notably, although treatment-related hypertension as an adverse event was reported in 43.8% of patients, only 3 cases were grade III or higher, and none of these cases led to discontinuation. A retrospective analysis exploring the association between elevated DBP and increased OS across 5 additional phase II axitinib studies similarly showed an association between transient increases in DBP and increased survival in other cancer types including non-small cell lung cancer, metastatic renal cell carcinoma, and thyroid cancer (40). Hypertension has been reported with other angiogenesis inhibitors (41, 42) and is usually manageable with standard antihypertensive agents (43).

Axitinib was generally well tolerated, with most adverse events of mild to moderate severity (grades I/II). Overall, adverse events were consistent with those previously reported for axitinib therapy (28, 29). Most were manageable through treatment interruptions, dose reductions, and/or standard medical interventions. Hypertension was reported in nearly half of patients, but, as previously noted, was generally grade I/II and did not interfere with therapy. The incidence of grade II proteinuria was also low (n = 2). One fatal bowel perforation assessed as treatment related occurred in a patient with abdominal and pulmonary cavity metastases. The most likely cause of the bowel perforation was tumor necrosis of metastatic masses with transmural invasion of the hollow organ. Similar events have been described with other antiangiogenic agents (44).

Analysis of soluble plasma proteins showed that axitinib therapy preferentially decreased sVEGFR-2 and sVEGFR-3 levels and increased plasma concentrations of VEGF. The same pattern of modulation has been reported for other agents targeting VEGF and VEGFRs (45), but multitargeted inhibitors of class III/V kinase receptors, such as sunitinib, also inhibit sKIT concentrations, reflecting a broader profile of signaling inhibition (34). Preclinical studies have shown that these changes are dose dependent and can correlate with antitumor activity, although they may occur in both naïve non–tumor-bearing and tumor-bearing mice (46). Changes that occur in naïve mice invoke a mechanism(s) independent of preclinical tumors. In this clinical trial, the use of soluble proteins was to serve as pharmacodynamic markers. The findings reported here provide clinical pharmacodynamic evidence of the selectivity of axitinib for twice a day for the majority of the study. However, experience with axitinib in other studies indicates that, in many cases, dose escalations beyond 5 mg twice a day are feasible. Intrapatient dose escalation to elicit a surrogate marker of response, reach maximum tolerated dose for an individual patient, and potentially increase response rate is currently common practice with cetuximab in colon cancer, following the EVEREST dose-escalation study (39). A similar strategy may enhance the efficacy of axitinib.

Hypertension has emerged as a potential marker for axitinib activity (40). In the current study, patients who experienced DBP of 90 mm Hg or higher (grade I hypertension) during treatment had a longer survival time than those who did not (median OS, 10.7 vs. 5.8 months, respectively). Notably, although treatment-related hypertension as an adverse event was reported in 43.8% of patients, only 3 cases were grade III or higher, and none of these cases led to discontinuation. A retrospective analysis exploring the association between elevated DBP and increased OS across 5 additional phase II axitinib studies similarly showed an association between transient increases in DBP and increased survival in other cancer types including non-small cell lung cancer, metastatic renal cell carcinoma, and thyroid cancer (40). Hypertension has been reported with other angiogenesis inhibitors (41, 42) and is usually manageable with standard antihypertensive agents (43).

Axitinib was generally well tolerated, with most adverse events of mild to moderate severity (grades I/II). Overall, adverse events were consistent with those previously reported for axitinib therapy (28, 29). Most were manageable through treatment interruptions, dose reductions, and/or standard medical interventions. Hypertension was reported in nearly half of patients, but, as previously noted, was generally grade I/II and did not interfere with therapy. The incidence of grade II proteinuria was also low (n = 2). One fatal bowel perforation assessed as treatment related occurred in a patient with abdominal and pulmonary cavity metastases. The most likely cause of the bowel perforation was tumor necrosis of metastatic masses with transmural invasion of the hollow organ. Similar events have been described with other antiangiogenic agents (44).

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VEGFRs relative to KIT at systemic exposures in patients with melanoma.

In conclusion, axitinib has clinical activity as a single agent in metastatic melanoma and was generally well tolerated. Axitinib preferentially decreased sVEGFR-2 and sVEGFR-3 plasma concentrations compared with sKIT levels, showing its selective targeting of VEGFRs. Further evaluation in combination with other agents is warranted for this disease and additional exploration of the potential relationship between transient increases in dBP of 90 mm Hg or higher, serum LDH levels, and clinical activity of axitinib will also be of interest.

Disclosure of Potential Conflicts of Interest

J. Lutzky received a commercial research grant from Pfizer Inc. O. Rixe has honoraria from speakers’ bureau of Pfizer Inc. D. McDermott is a consultant for Pfizer Inc. B. Rosbrook, A.C. Niethammer, and S. Kim are employees of Pfizer Inc. and B. Rosbrook and S. Kim own Pfizer stock. D. R. Shalinsky was a Pfizer employee during the time of this study and owns Pfizer stock; she is currently a paid contractor to Pfizer Inc. as a clinical scientist. J. Fruehauf, C.K. Brown, and J.-B. Meric have no conflict of interests to disclose.

Acknowledgments

The authors thank all of the participating patients and their families, as well as the investigators, research nurses, study coordinators, and operations staff. They also gratefully acknowledge technical and graphing support from Dr. Charles Harmon (Translational Oncology, Pfizer Oncology, San Diego, CA), technical support from Dr. Double-Bin You (Pfizer Oncology), as well as oversight of soluble protein and pharmacokinetic analyses by Brian Hee (Clinical Assay Group, Pfizer Inc.). Medical writing support, provided by Molly Heitz, ACIMED, Tytherington, United Kingdom, and manuscript submission and resubmission support, provided by Mariko Nagashima, PhD, UBC Scientific Solutions, Southport, CT, were funded by Pfizer Inc. This study was sponsored by Pfizer Inc.

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Received February 24, 2011; revised September 16, 2011; accepted September 20, 2011; published OnlineFirst October 5, 2011.

References


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Clin Cancer Res 2011;17:7462-7469. Published OnlineFirst October 5, 2011.

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