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A Phase I Study of the Anti-Activin Receptor-Like Kinase 1 (ALK-1) Monoclonal Antibody PF-03446962 in Patients with Advanced Solid Tumors

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Abstract

Purpose: Objectives of this dose-finding study were to determine the MTD and recommended phase II dose (RP2D) of the first-in-class anti-activin receptor-like kinase 1 (ALK-1) monoclonal antibody PF-03446962, and assess safety and antitumor activity in patients with advanced solid tumors.

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Disclosure of Potential Conflicts of Interest

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Experimental Design: This open-label, multicenter study was based on a 3+3 design. PF-03446962 was administered biweekly by intravenous infusion, at doses ranging from 0.5 to 15 mg/kg.

Results: Forty-four patients received treatment with PF-03446962. Dose-limiting toxicities observed during dose escalation included grade 3 increased amylase, grade 3/4 increased lipase, and grade 3/4 thrombocytopenia. The MTD was determined to be 10 mg/kg. The RP2D was set at 7 mg/kg for patients with advanced solid tumors, based on the observed safety, pharmacokinetics, and antitumor activity. The most-frequent treatment-related, all-grade adverse events included thrombocytope nia (20.5%), fatigue (15.9%), and nausea, increased amylase, and increased lipase (each 11.4%). Treatment-related telangiectasia was noted in 7% of patients, suggesting *in vivo* inhibition of the ALK-1 pathway. None of the deaths was deemed to be treatment-related. Three (6.8%) patients with advanced hepatocellular carcinoma, renal cell carcinoma, or non–small cell lung cancer achieved a partial response, and 12 (27.3%) patients had stable disease, across dose levels. Contrast-enhanced ultrasound analysis of tumor vascularity showed reduction in tumor perfusion in 2 patients with stable disease following treatment with PF-03446962.

Conclusions: The clinical activity demonstrated in this study points to PF-03446962 as a novel approach to antiangiogenic therapy, with manageable safety profile and single-agent, antitumor activity in patients with advanced solid tumors. *Clin Cancer Res; 1–9*.

Introduction

TGFβ regulates multiple biologic processes associated with tumor development and progression (1). TGFβ signals through the ubiquitously expressed type I activin-receptor like kinase (ALK)-5 and the more restricted receptors ALK-1 and endoglin (2). ALK-1 is a serine/threonine kinase receptor, preferentially expressed on proliferating endothelial cells, which binds with high affinity the bone morphogenetic protein (BMP) 9 and 10, both members of the TGFβ ligand super family (3–5). Endoglin is a type III TGFβ receptor required for vascular development and upregulated by endothelial cell activation in inflammation and tumor-associated angiogenesis (2).

Binding of BMP-9 to ALK-1 and formation of a complex with TGFβ and endoglin on endothelial cells of the tumor vasculature trigger downstream signaling, with activation of intracellular mediators, such as SMAD1/5 and induction of inhibitor of DNA binding (Id)1 expression (2, 3). Signaling through the SMAD1/5/ 8–Id1 pathway and transcriptional upregulation of proangiogenic factors induce endothelial cell differentiation, cell–cell interactions, and cell migration, resulting in vessel maturation during embryogenesis and neovascularization in tumors (2–5).

Loss-of-function mutations in the *ACVRL1 ALK-1* gene are associated with abnormal vasculature development, arterial venous malformations, and telangiectasia, as observed in type II hereditary hemorrhagic telangiectasia (HHT; Osler–Weber– Rendu syndrome), an autosomal dominant, vascular dysplasia syndrome. Abnormalities in endoglin expression have been reported in patients with type I HHT (6–9).

PF-03446962 is a first-in-class, fully human anti–ALK-1 monoclonal antibody (immunoglobulin G2). It has been shown in preclinical studies to selectively block binding of the ALK-1 ligands BMP-9 and TGFβ to ALK-1, and to inhibit recruitment of the coreceptor endoglin into the ALK-1 angiogenesis–signaling complex (10–12). PF-03446962 demonstrated antiangiogenic activity in human xenograft tumor models (12). It inhibited ALK-1 signaling and endothelial cell sprouting induced by proangiogenic factors, but did not affect VEGF signaling and VEGF-induced proliferation or migration of endothelial cells, thus providing evidence of a novel mechanism to inhibit angiogenesis (11).

Objectives of this first-in-human study were to estimate the MTD, define the recommended phase II dose (RP2D), and characterize the safety profile, pharmacokinetics (PK), and antitumor activity of PF-03446962 in patients with advanced solid tumors.

Patients and Methods

Study design and patient selection

This multicenter, open-label, single-arm, dose-finding, phase I study was conducted in patients with treatment-refractory solid tumors or with no available standard treatment, using a standard 3+3 design. Primary endpoints were to estimate the MTD and determine the RP2D for biweekly treatment with PF-03446962. Secondary endpoints included evaluation of the safety, PK profile, immunogenicity of PF-03446962, and preliminary assessment of its antitumor activity.

Patients with histologically or cytologically confirmed, treatment-refractory solid tumors, or advanced disease and either intolerance to or no available standard therapy were included in the study. Patients had to have Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1; a life expectancy ≥12 weeks; and adequate bone marrow (absolute neutrophil count ≥1,500/μL; platelets ≥100,000/μL, hemoglobin ≥9 g/dL), renal, and hepatic function. Eligible patients were enrolled in the dose escalation portion of this study at three sites, two in the United States and one in Italy.

Patients were excluded from the study if they had an active bleeding disorder, experienced cardiovascular events within 12 months of study entry, had a QT interval corrected for heart rate > 470 msec, uncontrolled hypertension, or active brain metastases. Patients with a history of HHT were excluded from this study. In addition, patients were not included if they required anticoagulant therapy (with the exception of low-dose, prophylactic anticoagulants) or had received chemotherapy, radiotherapy, or any investigational anticancer therapy within 4 weeks of study drug initiation.

The protocol was approved by the Institutional Review Boards of each participating institution. The study was conducted in compliance with the Declaration of Helsinki and the International Congress of Harmonization Good Clinical Practices guidelines. All patients provided signed informed consent. The study was supported by Pfizer and registered at Clinical-Trials.gov (NCT00557856).

Treatment and dose-limiting toxicity

PF-03446962 was administered as a 1-hour i.v. infusion on days 1 and 29, and then once every 2 weeks. The starting dose of 0.5 mg/kg was determined by a no-observed-adverse-effect level of 50 mg/kg in a repeat-dose toxicity study conducted in monkeys and adding a 100-fold additional safety factor. The dose level was escalated by 100% increments until a non– disease-related grade 2 or greater adverse event (AE) occurred in ≥1 patient within the same cohort or if 1 in 6 patients in the same cohort experienced a dose-limiting toxicity (DLT). Thereafter, dose escalation was continued in 50% increments until 2 of 3 or 2 of 6 patients experienced a DLT. Treatment was continued until disease progression, patient withdrawal, or unacceptable toxicity.

DLT was defined as any grade 3 or greater hematologic or nonhematologic AE occurring during the first 6 weeks possibly related to treatment with PF-03446962.

Assessments

Safety.—Physical examinations were performed at screening; on days 1, 8, 15, and 22 of cycle 1; day 1 of subsequent cycles; at the end of treatment; and at follow-up visit. AEs were continuously monitored and graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Pharmacokinetics.—Blood samples were collected for PK assessments on days 1, 3, 5, 8, 11, 15, and 22 of the first cycle, and on day 1 of the following cycles, until cycle 12. Patient samples were assayed for PF-03446962 serum concentrations (QPS LLC) using a validated chemiluminescence enzyme-linked immunosorbent assay. The lower limit of PF-03446962 quantification was 100 ng/mL.

Antitumor activity.—Objective tumor assessments were performed by CT or MRI at screening, 6 weeks after the first dose of PF-03446962, and approximately every 6 weeks thereafter, according to Response Evaluation Criteria in Solid Tumors, version 1.0. Endpoints included complete or partial response and stable disease, which were confirmed by tumor imaging.

Tumor vascular activity.—Three consecutive patients were examined with contrast-enhanced ultrasound (CE-US) to evaluate its feasibility in assessing early tumor response to treatment. All 3 patients had liver lesions accessible to routine gray-scale ultrasound imaging. CE-US scans were obtained for each patient at baseline (2 scan sets/patient to determine variability) and on days 1 and 15 after first dose. Sonography and image analysis were performed with an iU22 scanner and Q-Lab software, respectively (Philips Medical Systems). Additional details are described online in Supplementary Methods.

Statistical analyses

The number of patients to be enrolled at each dose level and the number of dose cohorts were dependent on the safety profile observed during the course of the study. Descriptive statistics were used throughout the study. A 90% exact confidence interval was calculated for the response rate.

Results

Patients

A total of 44 patients were enrolled and treated at doses ranging from 0.5 to 15 mg/kg: Patient cohort enrollment, demographics, and disease characteristics are presented in Table 1. Twelve of the 44 patients on study had colorectal cancer; 5 each had liver, renal/adrenal, or lung cancer; and 4 each had other gastrointestinal cancers (pseudomyxoma peritonei, gastrointestinal stromal tumor, and esophageal squamous cell carcinoma) or thyroid cancer. Patients with pancreatic (n = 3), gynecologic (n = 2), or prostate (n = 1) cancer, sarcoma (n = 2), or malignant thymoma (n = 1) were also enrolled in this trial.

Ninety-six percent of patients had stage IV disease at the time of diagnosis; the majority (66%) had ECOG PS 1. All patients had received prior systemic, anticancer treatment, and 71% had been treated with three or more regimens.

DLT and safety

All patients received ≥1 dose of study drug and were thus evaluable for DLTs, which included DLTs observed in cycles 1 and 2, and during follow-up if the AE occurred after cycle 2, up to day 1 of cycle 3. DLTs included grade 3 increased amylase and lipase in 1 patient in the 2-mg/kg group (n = 6), grade 4 thrombocytopenia in 1 patient in the 6.75-mg/kg group (n = 8), grade 3 thrombocytopenia in 1 patient in the 10-mg/kg group (n = 7), and grade 3 increased amylase/grade 4 increased lipase and grade 3 thrombocytopenia in 1 patient each in the 15-mg/kg group (n = 6; Table 2). The MTD for biweekly i.v. administration of PF-03446962 was therefore estimated to be 10 mg/kg.

All treated patients reported a treatment-emergent, all-cause AE across dose levels, of which the most frequent (% patients) were fatigue (29.5%), nausea (29.5%), and thrombocytopenia (22.7%; Table 3). Twenty-nine (65.9%) patients experienced a treatment-related AE. The most frequent (% patients) treatment-related AEs included thrombocytopenia (20.5%), fatigue (15.9%), and nausea, increased amylase, and increased lipase (all 11.4%; Table 3). In almost all patients, a reduction in platelets (“trough”) was observed in cycle 1 between days 8 and 15, with a trend to recovery. The occurrence of thrombocytopenia was not associated with bleeding. The observed elevations in pancreatic enzymes were limited to laboratory alterations and were transient in nature. Skin telangiectasia was reported in 4 (9.1%) patients and deemed related to study treatment in 3 (6.8%) patients. Examples of telangiectasia observed in patients treated with PF-03446962 are shown in Supplementary Fig. S1.

Nineteen (43.2%) patients experienced grade 3 to 4 AEs, which were considered treatment-related in 8 (18.2%) patients. In the 6.75-mg/kg group, later identified as the RP2D, 1 patient experienced grade 4 treatment-related thrombocytopenia and 1 patient each had a grade 3 treatment-related pulmonary embolism, increased alanine aminotransferase, and increased aspartate aminotransferase.

None of the 3 deaths reported (2 at 6.75-mg/kg and 1 at 15-mg/kg doses) were considered to be treatment related. They were due to disease progression in 1 patient each with renal cell carcinoma, non–small cell lung cancer, and adenocarcinoma of the pancreas.

Two (4.5%) patients had a dose reduction owing to AEs (treatment-related in 1 patient), and 15 (34.1%) had temporary discontinuations due to AEs (treatment-related in 8 patients). All patients were discontinued from the study, mostly owing to disease progression (n = 25; 57%). Treatment was permanently discontinued in 10 (23%) patients owing to all-cause AEs and in 5 (11.4%) because of treatment-related AEs. The treatment-related AEs (grade 2–4 thrombocytopenia and grade 3 pulmonary embolism) observed in these 5 patients resolved following treatment discontinuation. Treatment was temporarily discontinued in 8 patients and the dose reduced in 1 patient, owing to treatment-related AEs, which included grade 1–3 increased amylase and grade 3–4 increased lipase (n = 3), grade 3 intestinal obstruction (n = 1), grade 2 cytokine release syndrome (n = 1), grade 1–2 thrombocytopenia (n = 1), grade 1 abdominal pain, grade 1–3 elevations in liver enzymes, grade 1 hypoalbuminemia (n = 1), and grade 1–2 asthenia (n = 1). The median duration of treatment with PF-03446962 was 28 to 84 days across dose levels (range, 28 to 490 days). Duration of treatment for each patient is shown in Fig. 1A by dose level.

Pharmacokinetics

Median serum concentration–time profiles following single-dose administration of PF-03446962 in cycle 1 are shown in Fig 2, for all dose levels. The PK parameters for all dose levels are summarized in Supplementary Table S1.

Serum concentrations of PF-03446962 declined in a bi-exponential manner over the course of the treatment interval. PF-03446962 was slowly eliminated from the circulation. Geometric mean clearance values appeared to decrease with an increase in dose, from 0.077 L/hr for 0.5 mg/kg (lowest dose) to 0.0117 L/hr for 15 mg/kg (highest dose). The terminal half-life of PF-03446962 ranged from 2.7 to 7.4 days for the 0.5- to 2.0-mg/kg doses and 13.6 to 18 days for the 3.0- to 15-mg/kg doses.

Antitumor activity

Three (6.8%) patients achieved a partial response following treatment with PF-03446962: 1 in the 2-mg/kg and 2 in the 10.0-mg/kg groups. All 3 patients had a confirmed partial response and all 3 had disease progression at study entry, following prior treatment failure. No complete responses were observed in this study (Supplementary Table S2). Twelve (27.3%) patients had stable disease across dose levels (0.5- to 15-mg/kg), which lasted >16 weeks in 6 patients (Fig. 1B).

In the 2-mg/kg group, the patient with a partial response had a primary diagnosis of metastatic hepatocellular cancer previously treated with sorafenib. This patient developed a partial response after 4 cycles of treatment with PF-03446962, with response duration of 44 days. The second patient with a partial response (10-mg/kg group) had metastatic clear cell renal carcinoma previously treated with sunitinib, sorafenib, and everolimus. The patient developed a partial response after 5 cycles of treatment with PF-03446962, and duration of response was 325 days. The third patient with a partial response (10-mg/kg group) had *KRAS* mutation–positive non–small cell lung cancer. Prior treatments included surgery and multiple lines of chemotherapy. This patient had a partial response after 8 cycles of treatment with PF-03446962 and duration of response was 308 days.

CE-US analysis

Three patients with colon cancer metastatic to the liver completed CE-US examinations; all had good reproducibility at baseline. All 3 patients had received prior therapy with bevacizumab, and treatment had been discontinued for disease progression, completed treatment, or unknown reason (1 patient each). Two of the 3 patients (with SD for 21 and 165 days, respectively) demonstrated well-perfused target liver lesions on pretreatment imaging, as characterized by high-peak CE (25 dB, 15 dB), microvascular density (22.7 dB, 21.5 dB), and blood-flow velocity (1.1 1/sec, 0.52 1/sec). The third patient, with progressive disease 35 days after PF-03446962 treatment initiation and prior bevacizumab failure, had a target lesion with decreased perfusion on the pretreatment scan, compared with patients with stable disease, with relatively low-peak CE (8.9 dB), low-microvascular density (1.9 dB), and slow blood-flow velocity (0.04 1/sec).

Both patients with stable disease showed a substantial reduction in lesion perfusion on day 15 after first dose. Peak CE had decreased by 32% (to 17 dB) and 33% (to 10 dB), respectively; microvascular density by 40% (to 13.7 dB) and 56% (to 9.4 dB); and blood-flow velocity by 36% (to 0.7 1/sec) and 35% (to 0.34 1/sec; Fig. 3). In contrast, the patient with progressive disease showed an increase in CE-US parameters of tumor perfusion on day 15. Peak CE had increased by 27% (to 11.3 dB), microvascular density by 68% (to 3.2 dB), and blood-flow velocity had increased 4-fold (to 0.2 1/sec). None of the patients demonstrated measurable (>5%) change in tumor size.

Discussion

We report findings from the first-in-human study of the anti– ALK-1 monoclonal antibody PF-03446962 in patients with advanced solid tumors. PF-03446962 was generally well tolerated, and the MTD for i.v. administration was estimated to be 10 mg/kg. The PK profile observed in this study supports a biweekly regimen for administration of PF-03446962. None of the treated patients showed positivity for anti–PF-03446962 antibodies (data not shown).

Treatment with PF-03446962 was associated with a manageable safety profile. The most frequent treatment-related AEs included thrombocytopenia, fatigue, and nausea, as well as increased amylase and lipase levels. Grade 3 and 4 thrombocytopenia was noted in 4 (9.1%) and 1 (2.3%) patients, respectively. Thrombocytopenia was generally transient and not associated with bleeding episodes in PF-03446962–treated patients. The patient with grade 4 thrombocytopenia had thyroid cancer and a platelet count at baseline within the inclusion criteria (≥100,000/μL). No bleeding episodes were reported in this patient, and the presence of antiplatelet antibodies was excluded. In addition, a bone marrow biopsy confirmed normal marrow elements (data not shown), suggesting that the observed thrombocytopenia did not result from dose-dependent bone marrow suppression. No further investigations were conducted to identify the mechanism(s) underlying platelet reduction following administration of PF-03446962. The amylase and lipase elevations observed in several patients were limited to reversible laboratory alterations and were not associated with clinical pancreatitis. In addition, patients treated long term (~1 year) with PF-03446962, who achieved stable disease and had pancreatic enzymes elevation, were asymptomatic and

did not present any clinical manifestation of pancreatitis. These observations are consistent with results from prior studies in animal models, which had shown minimal to moderate depletion of zymogen granules in pancreatic acinar cells following exposure to PF-03446962. This finding indicated reversibility by the end of the recovery period, with no evidence of degeneration or necrosis of acinar cells in affected animals, nor any indication of exocrine pancreatic insufficiency (unpublished data). Permanent study drug discontinuations due to treatment-related AEs occurred in approximately 11% of patients.

Telangiectasia, which is associated with mutations in the *ALK-1* gene in patients affected by HHT type 2, was observed in approximately 9% of patients, and considered to be treatment-related in approximately 7%, suggesting target engagement and *in vivo* inhibition of ALK-1 by PF-03446962 (9–11). A similar finding of treatment-related telangiectasia has been reported in clinical studies of an ALK-1 receptor fusion protein (dalantercept) and an endoglin-neutralizing antibody (TRC105) in patients with advanced cancer (13–16). Of note, hyponatremia was reported following treatment with dalantercept, but not with PF-03446962 (13, 15). Peripheral edema, observed with dalantercept, was not dose limiting for treatment with PF-03446962, and it was noted only in a minority of PF-03446962–treated patients (13, 15). Furthermore, hypertension, proteinuria, and bleeding, known to be associated with administration of the VEGF inhibitor bevacizumab, were not frequently observed with PF-03446962 (17).

Preliminary evidence of clinical benefit from treatment with single-agent PF-03446962 was noted in this dose-escalation study, with three partial responses (1 with 2-mg/kg and 2 with 10-mg/kg doses). The C_{max} and AUCs observed in the patient treated with PF-03446962 2 mg/kg were similar to those of other patients treated in the same dose cohort. The sample size for this trial was too small to determine any conclusive relationship between exposure and response. The duration of response in these patients ranged from 44 to 325 days. Twelve (27.3%) patients had stable disease. Although the MTD was 10 mg/kg biweekly, the RP2D for PF-03446962 was determined to be 7 mg/kg biweekly, based on the safety, tolerability, and PK results, as well as the antitumor activity observed in this study. In addition, the half-life at this dose level was approximately 10 days, and the concentrations observed well exceeded the efficacious concentration (EC_{50}) derived from preclinical studies following a PF-03446962 dose of 7 mg/kg biweekly. Of note, the dose of 7 mg/kg biweekly was selected as the RP2D to be used in future studies to prevent possible effects on platelets in a potentially fragile population, such as patients with hepatocellular carcinoma, which was the clinical setting chosen for further development of this investigational agent. Preliminary analysis of the results obtained from evaluation of PF-03446962 in an expansion cohort of patients with hepatocellular carcinoma confirmed 7 mg/kg biweekly as the RP2D for the treatment of patients with advanced solid tumors (18, 19).

Dosing of therapeutic monoclonal antibodies was generally based on body size, with the consideration that body size–based dosing would reduce intersubject variability in drug exposure. However, recent studies suggest that body size has a small contribution to variability in key PK parameters of most monoclonal antibodies, on the basis of population PK models (20). Therefore, our dosing strategy in clinical development will further assess fixed dosing, which provides many practical advantages, based on combined knowledge of

the body weight effect on PK, safety, and efficacy from early clinical studies with PF-03446962.

The preliminary CE-US results are encouraging and indicate that pretreatment CE-US has the potential to become a useful tool to select patients with vascular tumors potentially more responsive to treatment than hypovascular ones. In addition, CE-US has a substantial potential to serve as a noninvasive tool to predict antiangiogenic tumor response as early as 15 days after treatment initiation. In the small group tested ($n = 3$), 2 patients with stable disease following treatment had actively perfused tumors at baseline and demonstrated substantial (32%–56%) reduction in tumor perfusion parameters 2 weeks after the first dose of PF-03446962. A patient with progressive disease following treatment had a poorly perfused hypovascular tumor at baseline and demonstrated an increase in perfusion on day 15. Although promising, results obtained with CE-US imaging are based only on 3 patients, and future prospective study of this imaging biomarker will be required to fully assess its clinical utility. Results of an analysis of circulating endothelial cells (CEC) did not allow identification of consistent trends in CEC (data not shown). Studies are in progress to identify tumor and circulating biomarkers of efficacy.

Of note, PF-03446962 showed activity in patients with disease progression following prior antiangiogenic therapy. Two of the patients with partial response to PF-03446962 had primary diagnoses of metastatic hepatic cancer and renal cell carcinoma, respectively, and had received prior treatment with angiogenesis inhibitors, including sorafenib. The third patient with a partial response had previously received treatment for non–small cell lung cancer, including multiple cytotoxic agents and sunitinib.

There is preclinical evidence suggesting that ALK-1 inhibition may augment the tumor control seen with VEGF inhibitors (2, 12). At the vascular level, ALK-1 blockade has a distinct phenotype from that of VEGF inhibition. Treatment with bevacizumab results in large, open vessels positive for both CD31 and desmin, mimicking a normalized vascular phenotype. ALK-1 inhibition, on the other hand, leads to near absence of CD31 in large vessels, demonstrating a loss of the endothelial cell layer. The combination of VEGF blockade and ALK-1 inhibition results in marked vascular disruption and demonstrated synergistic antitumor activity in murine models (2, 12). The clinical observation of antitumor activity in patients treated with PF-03446962 following prior VEGF-inhibitor therapy provides the rationale for further development of PF-03446962 in combination studies with other molecularly targeted or cytotoxic agents in patients with solid tumors. In conclusion, PF-03446962 represents a new strategy in antiangiogenic therapy, with manageable side effects and intriguing single-agent activity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Translational Relevance

ALK-1 is a serine/threonine kinase receptor involved in vessel maturation during embryogenesis and tumor neovascularization. PF-03446962, a first-in-class, fully human anti– ALK-1 monoclonal antibody, selectively blocks binding of the ALK-1 ligands bone morphogenetic protein-9 and TGFβ, and inhibits recruitment of the coreceptor endoglin. PF-03446962 has demonstrated antiangiogenic activity in human xenograft tumor models. In this first-in-human study, treatment with single-agent PF-03446962 was generally well tolerated; the MTD was estimated to be 10 mg/kg and the recommended phase II dose set at 7 mg/kg. The pharmacokinetic profile observed supports biweekly administration of PF-03446962. Treatment was associated with a manageable safety profile and preliminary evidence of clinical activity. A substantial reduction in tumor perfusion was observed by contrast-enhanced ultrasound in 2 patients with actively perfused tumors at baseline who achieved stable disease following treatment. ALK-1 inhibition by PF-03446962 represents an intriguing new strategy for antiangiogenic therapy in patients with solid malignancies.

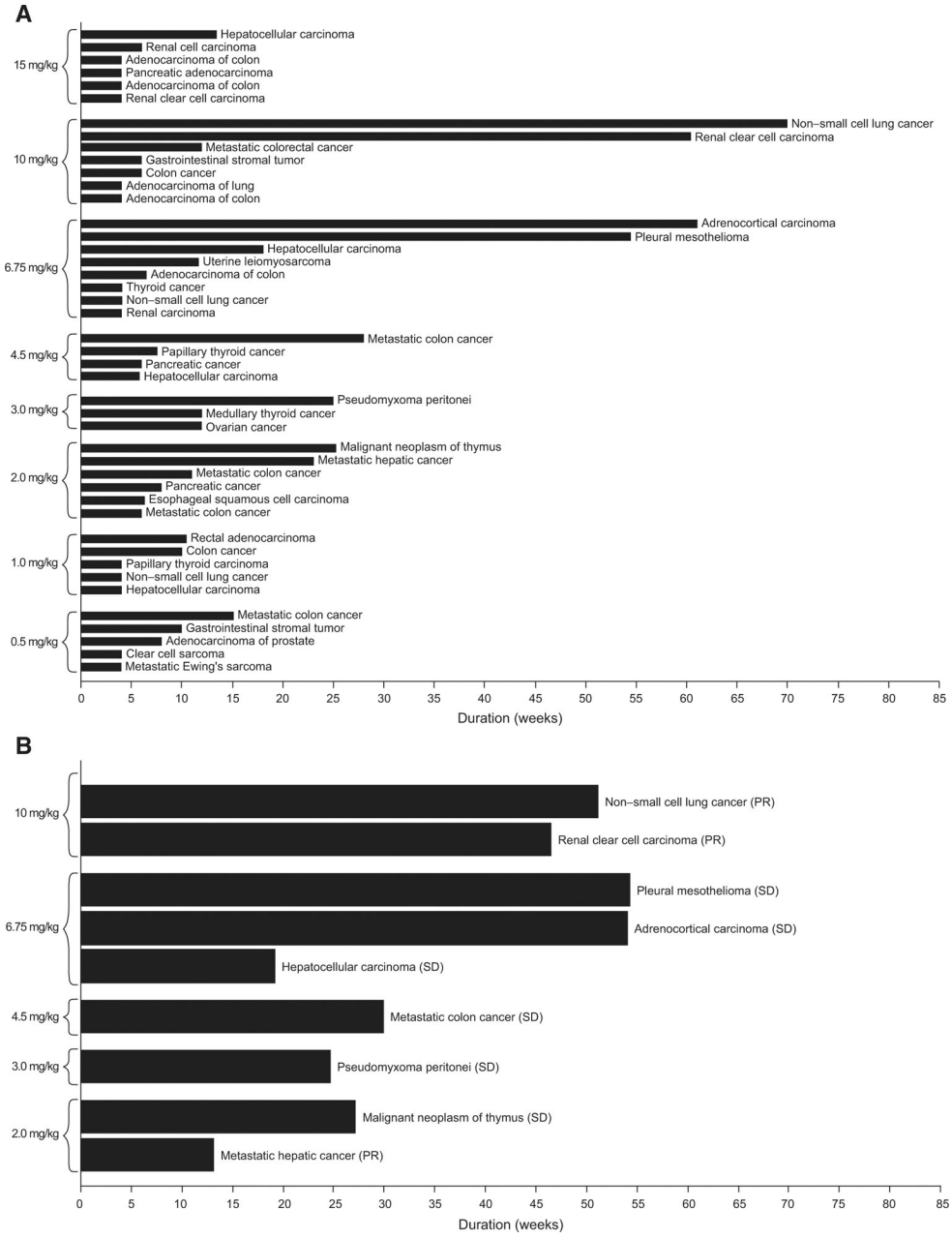

Figure 1.

Duration of treatment (top) and duration of response or stable disease ≥16 weeks (bottom) by dose level in individual patients receiving PF-03446962. PR, partial response; SD, stable disease ≥16 weeks.

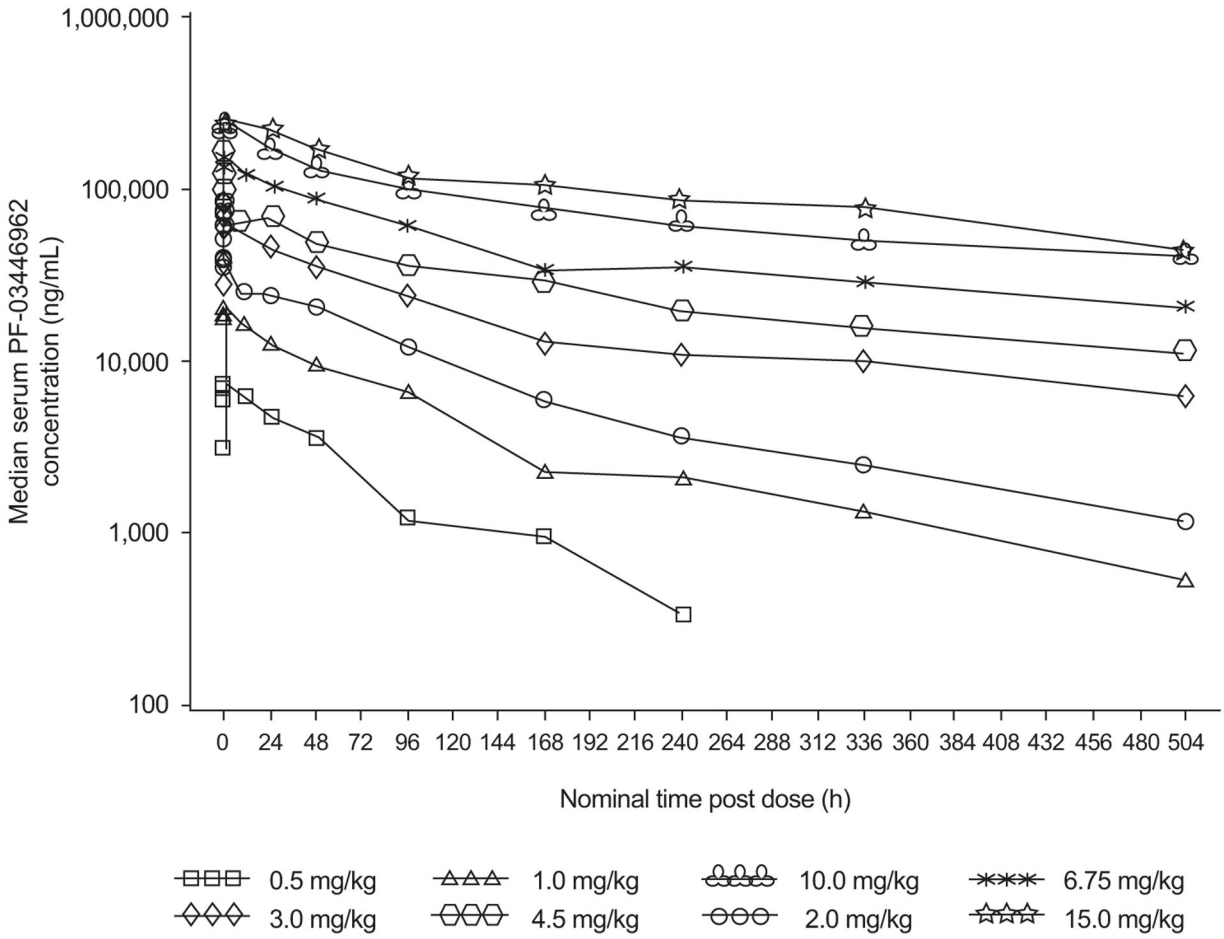

Figure 2.
Median serum concentration of PF-03446962 following single-dose administration (cycle 1).

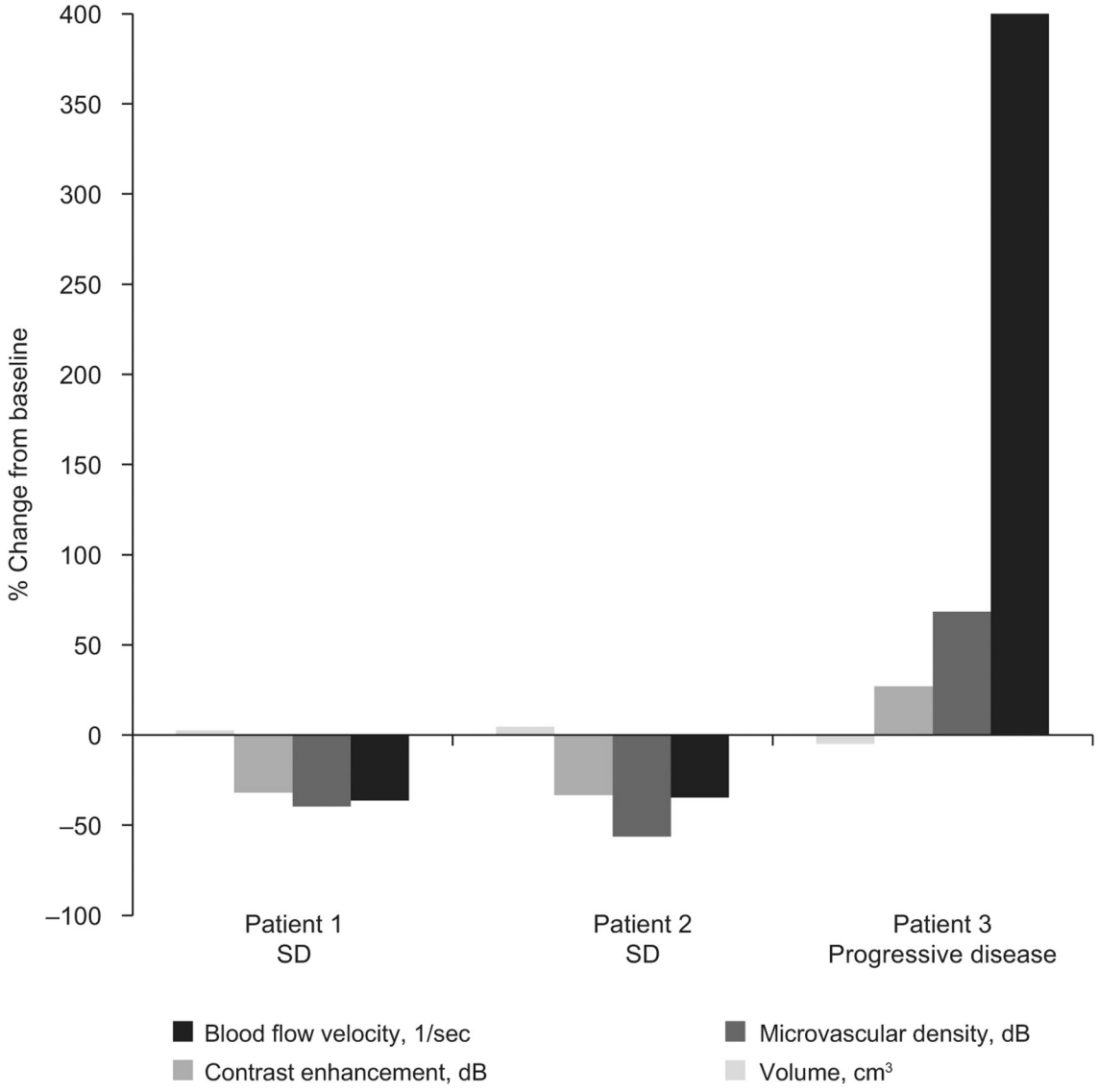

Figure 3.
Changes in tumor volume and perfusion by CE-US following treatment with PF-03446962 (day 15).

Table 1.

Patient baseline demographics and clinical characteristics

	PF-03446962 dosage, mg/kg								
Parameter[a]	**0.5 *n* = 5**	**1.0 *n* = 5**	**2.0 *n* = 6**	**3.0 *n* = 3**	**4.5 *n* = 4**	**6.75 *n* = 8**	**10.0 *n* = 7**	**15.0 *n* = 6**	**Total *N* = 44**
Male, *n* (%)	3 (60.0)	2 (40.0)	4 (66.7)	2 (66.7)	2 (50.0)	5 (62.5)	4 (57.1)	3 (50.0)	25 (56.8)
Female, *n* (%)	2 (40.0)	3 (60.0)	2 (33.3)	1 (33.3)	2 (50.0)	3 (37.5)	3 (42.9)	3 (50.0)	19 (43.2)
Median age, y	57.0	62.0	65.5	55.0	65.5	62.5	58.0	61.5	61.5
Range	44–80	34–70	48–69	46–61	56–68	47–77	42–80	48–74	34–80
Race, *n* (%)									
White	4 (80.0)	5 (100.0)	6 (100.0)	3 (100.0)	3 (75.0)	8 (100.0)	7 (100.0)	6 (100.0)	42 (95.5)
Black	0	0	0	0	1 (25.0)	0	0	0	1 (2.3)
Asian	0	0	0	0	0	0	0	0	0
Other	1 (20.0)	0	0	0	0	0	0	0	1 (2.3)
ECOG PS, *n* (%)									
0	2 (40.0)	1 (20.0)	3 (50.0)	3 (100.0)	1 (25.0)	1 (12.5)	3 (42.9)	0	14 (31.8)
1	3 (60.0)	4 (80.0)	3 (50.0)	0	3 (75.0)	6 (75.0)	4 (57.1)	6 (100.0)	29 (65.9)
2	0	0	0	0	0	1 (12.5)	0	0	1 (2.3)
Disease stage, *n* (%)									
Stage III	0	1 (20.0)	0	0	0	0	0	0	1 (2.3)
Stage IV	5 (100)	4 (80.0)	6 (100.0)	3 (100.0)	3 (75.0)	8 (100.0)	7 (100.0)	6 (100.0)	42 (95.5)
Other	0	0	0	0	1 (25.0)	0	0	0	1 (2.3)
Measurable disease, *n* (%)									
Yes	5 (100.0)	5 (100.0)	6 (100.0)	3 (100.0)	4 (100.0)	7 (87.5)	7 (100.0)	6 (100.0)	43 (97.7)
No	0	0	0	0	0	1 (12.5)	0	0	1 (2.3)
Number of prior Antiangiogenic therapies, *n* (%)									
0	3 (60.0)	2 (40.0)	3 (50.0)	2 (66.6)	2 (50.0)	4 (50.0)	0	1 (16.6)	17 (38.6)
1	2 (40.0)	1 (20.0)	1 (16.6)	0	1 (25.0)	3 (37.5)	2 (28.6)	1 (16.6)	11 (25.0)
2	0	1 (20.0)	1 (16.6)	1 (33.3)	1 (25.0)	0	2 (28.6)	3 (50.0)	9 (20.4)
3	0	1 (20.0)	1 (16.6)	0	0	1 (12.5)	2 (28.6)	0	5 (11.4)
4	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	1 (14.2)	1 (16.6)	2 (4.6)

[a] Twelve patients had colorectal cancer, 5 each had liver cancer, renal/adrenal cancer (including adrenocortical adenoma, renal cancer, renal cell carcinoma, and clear cell renal cell carcinoma), or lung cancer (lung adenocarcinoma, pleural mesothelioma, and non–small cell lung cancer); 4 each had other gastrointestinal cancers (pseudomyxoma peritonei, gastrointestinal stromal tumor, and esophageal squamous cell carcinoma) or thyroid cancer; 3 had pancreatic cancer; 2 each had gynecologic cancer (uterine leiomyosarcoma and ovarian cancer) or sarcoma; and 1 each had prostate cancer or malignant thymoma.

Table 2.

Dose-limiting toxicities

PF-03446962 (mg/kg)	No. of patients[a]	No. of DLTs	DLT
0.5	5	0	–
1.0	5	0	–
2.0	6	1	Grade 3 increased amylase and lipase
3.0	3	0	–
4.5	4	0	–
6.75	8	1	Grade 4 thrombocytopenia
10.0	7	1	Grade 3 thrombocytopenia
15.0	6	2	Grade 3 increased amylase and grade 4 increased lipase
			Grade 3 thrombocytopenia

[a]Due to an extended DLT observational period initially required by the study design; several patients dropped out earlier, thus requiring replacement.

Table 3.

Treatment-emergent AEs in >3 patients

	***N* = 44**	
Adverse Event	**All-Causality *n* (%)**	**Treatment-Related *n* (%)**
Any AE	44 (100)	29 (65.9)
Fatigue	13 (29.5)	7 (15.9)
Nausea	13 (29.5)	5 (11.4)
Thrombocytopenia	10 (22.7)	9 (20.5)
Cough	9 (20.5)	0
Asthenia	8 (18.2)	1 (2.3)
Blood alkaline phosphatase increased	8 (18.2)	4 (9.1)
Dyspnea	7 (15.9)	0
Edema peripheral	7 (15.9)	1 (2.3)
Abdominal pain	6 (13.6)	1 (2.3)
Amylase increased	6 (13.6)	5 (11.4)
Headache	6 (13.6)	3 (6.8)
Lipase increased	6 (13.6)	5 (11.4)
Vomiting	6 (13.6)	1 (2.3)
Anemia	5 (11.4)	2 (4.5)
Constipation	5 (11.4)	0
Hyperglycemia	5 (11.4)	0
Upper respiratory tract infection	5 (11.4)	0
Alanine aminotransferase increased	4 (9.1)	4 (9.1)
Arthralgia	4 (9.1)	0
Decreased appetite	4 (9.1)	0
Diarrhea	4 (9.1)	0
Hypertension	4 (9.1)	3 (6.8)
Hyperuricemia	4 (9.1)	3 (6.8)
Hypokalemia	4 (9.1)	1 (2.3)
Pyrexia	4 (9.1)	0
Telangiectasia	4 (9.1)	3 (6.8)