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ORIGINAL REPORT

Phase I Clinical and Pharmacokinetic Study of the Novel Raf Kinase and Vascular Endothelial Growth Factor Receptor Inhibitor BAY 43-9006 in Patients With Advanced Refractory Solid Tumors

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ABSTRACT

Purpose

BAY 43-9006 is a novel dual-action Raf kinase and vascular endothelial growth factor receptor inhibitor that inhibits tumor cell proliferation and angiogenesis. This study established the safety and pharmacokinetics of BAY 43-9006 in 69 patients with advanced refractory solid tumors.

Patients and Methods

BAY 43-9006 (50 to 800 mg) was administered once or twice daily on a varying weekly schedule. Pharmacokinetic sampling was performed in all patients; preliminary tumor response was also assessed. The effect of BAY 43-9006 on phorbol myristate acetate–stimulated ERK phosphorylation in peripheral blood lymphocytes was studied using flow cytometry.

Results

Mild to moderate diarrhea was the most common (55%) treatment-related adverse event. The maximum-tolerated dose was 400 mg bid continuous. Dose-limiting toxicities were grade 3 diarrhea and fatigue at 800 mg bid, and grade 3 skin toxicity at 600 mg bid. BAY 43-9006 pharmacokinetics were highly variable for single and multiple dosing, and toxicity did not appear to be dose dependent. Significant decreases of phorbol myristate acetate–stimulated ERK phosphorylation ($P < .01$) were identified at doses $\geq$ 200 mg bid continuous. Forty-five patients were assessable for efficacy; one patient had a partial response (hepatocellular carcinoma at 400 mg bid continuous), 25 patients had stable disease, with eight lasting $>$ 6 months and five for $>$12 months. Eighteen patients had progressive disease, and tumor response could not be evaluated in one patient.

Conclusion

Oral BAY 43-9006 was well tolerated and appeared to provide some clinical benefits. Based on the results of this study, BAY 43-9006 at 400 mg bid continuous is recommended for ongoing and future studies.

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INTRODUCTION

BAY 43-9006 is a novel dual-action Raf kinase and vascular endothelial growth factor (VEGF) inhibitor that prevents tumor growth by combining two anticancer activities: inhibition of tumor cell proliferation and tumor angiogenesis. Activation of Ras family members, including Raf kinase, is critical for the diversification of signal transduction pathways involved in the normal regulation of the cell cycle, gene expression, cellular proliferation, differentiation, membrane trafficking and secretion, and motility.[1-3] Ras relays cytokine and growth factor information from the cell surface to

the nucleus by initiating several signaling cascades. The best characterized of these is the Raf/MEK/ERK pathway, which mediates cellular proliferation, differentiation, and transformation.[4-6] Constitutive activation of the components of this pathway has been demonstrated in transformed cell lines and primary tumors,[7-11] and inhibition of these downstream effectors could diminish deregulated proliferation in malignant cells.

Survival and metastasis of solid tumors depend largely on the two angiogenic growth factors—basic fibroblast growth factor and VEGF—which have been shown to differentially activate Raf. Targeted delivery of a mutant form of Raf-1 to tumor blood vessels inhibits angiogenesis and has also been shown to lead to regression of established tumors.[12]

BAY 43-9006 is an orally available, potent, small-molecule inhibitor of c-Raf-1 and wild-type and mutant (V599E) B-Raf.[13] In vitro, BAY 43-9006 reduced MEK and ERK phosphorylation without directly inhibiting MEK or ERK kinase activity.[14,15] BAY 43-9006 also inhibited phosphorylation and, therefore, activation of several receptor tyrosine kinases involved in angiogenesis and tumor progression, including VEGF receptor (VEGFR) -2, VEGFR-3, platelet-derived growth factor receptor beta (PDGFR-β), Flt3, and c-kit, as well as p38α, a member of the mitogen-activated protein kinase (MAPK) family.[13] BAY 43-9006 has demonstrated significant and broad activity against human tumor xenograft models of colon, pancreatic, and non small-cell lung origin with mutations in B-Raf or K-Ras.[16] In addition, BAY 43-9006 significantly inhibited neovascularization in xenograft models of two human colon cancers (HT-29 and Colo205) and human breast cancer (MDA-MB-231).[13]

In all human xenograft studies, tumor growth suppression was maintained during the dosing period, and some tumor regressions were observed.[14,16] Prolonged exposure to BAY 43-9006 was associated with increased antitumor activity in animal models; BAY 43-9006 treatment for 30 consecutive days in mice harboring DLD-1 colon tumors produced approximately three times the growth delay of a single 10-day course of treatment.[14]

This phase I clinical trial was initiated to determine the dose-limiting toxicities (DLTs), maximum-tolerated dose (MTD), and pharmacokinetics of oral daily BAY 43-9006. Preliminary antitumor activity and inhibition of PMA-stimulated ERK-phosphorylation in peripheral blood lymphocytes (PBLs) of treated patients were also assessed.

PATIENTS AND METHODS

Patient Selection

Eligible patients were between 18 and 75 years of age, with a life expectancy of at least 12 weeks, and a solid tumor that was refractory to standard treatment, or for which no standard therapy existed. Patients were required to have Eastern Cooperative Oncology Group performance status ≤ 2. All patients had received previous treatment and had assessable disease.

Eligibility requirements included the following: adequate bone marrow function (neutrophils $\geq 1{,}500/\mu L$, hemoglobin ≥ 9.0 g/dL, and platelets $\geq 100{,}000/\mu L$), serum creatinine < 1.5 mg/dL, total bilirubin < 1.5 mg/dL, AST $< 2\times$ the upper limit of normal ($< 5\times$ the upper limit of normal in the presence of liver metastases), and no prolongation of the prothrombin time or activated partial thromboplastin time.

Patients were excluded from the study if they had clinically evident severe cardiovascular disorders (eg, myocardial infarction < 6 months previously, chronic heart failure [New York Heart Association grade III or IV], or severe cardiac rhythm disturbances); received chemotherapy or radiotherapy within 4 weeks of study entry; had clinical evidence of CNS metastases; were HIV seropositive; were pregnant or lactating; were considered a poor medical risk because of other nonmalignant disease or active infections; or had psychological or social problems that could limit study participation. All patients received information regarding the purpose and conduct of this study, and provided written informed consent in accordance with federal and institutional guidelines.

Study Design

This was a single-center (University Hospital, Essen, Germany), phase I, dose-escalation study to establish the MTD and DLTs of oral BAY 43-9006. Administration of BAY 43-9006 continued until the occurrence of unacceptable toxicity, withdrawn consent, disease progression, or death. Treatment was also discontinued if tumor progression occurred, and a final visit took place within 2 weeks of establishing progression. Patients with complete response, partial response (PR), or stable disease (SD) at the end of the initial 4-week treatment were eligible to receive continuous BAY 43-9006 therapy until disease progression or unacceptable toxicity occurred. The actual dose of BAY 43-9006 administered during this extension was at the investigator's discretion.

In this study, initial dosing was performed on day 1 of a weekly cycle. The starting dose was based on preclinical data. In a 4-week repeated dose study in dogs, enhanced ALT and LDH were observed starting at doses of 10 mg/kg BAY 43-9006 per day. The oral bioavailability for BAY 43-9006 was estimated to be similar in humans, therefore, 50 mg BAY 43-9006 was considered to be a safe starting dose for phase I trials. Because of limited bioavailability beyond 400 mg single dosing, further dose escalation was performed by bid application and continued by doubling the number of treatment days per week (day 1, days 1 and 2, days 1 through 4, continuous dosing). Since 400 mg bid continuous dosing was initially not considered the MTD, dose escalation occurred until 600 mg and 800 mg, respectively. Because of DLTs, the dose level 400 mg bid continuous dosing was eventually recommended for further phase II testing.

Since all dose levels lower than 100 mg bid continuous dosing (ie, all noncontinuous dose levels) were associated with low bioavailability, we pooled these early dose levels and summarized the data for safety and preliminary efficacy as noncontinuous dosing schedules. BAY 43-9006 tosylate was supplied as 50-mg tablets.

Three patients were initially enrolled in each cohort; in the absence of a DLT at the end of a 4-week treatment cycle, the next

cohort of three patients was enrolled. If any patient developed a DLT, three additional patients were enrolled at that dose level.

Adverse events (AEs) were assessed at the end of each cycle, and graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.[17] Dose escalation proceeded until the MTD was reached. The MTD was defined as the dose level below that at which at least two out of six patients experienced a DLT, which was defined as grade 3 or 4 nonhematologic toxicity, febrile neutropenia, or grade 4 neutropenia lasting at least 4 days, or grade 3 or 4 thrombocytopenia.

Patient Evaluation

Physical examinations and hematologic/biochemical laboratory evaluations were performed weekly. Baseline objective tumor measurements were performed up to 2 weeks before the start of therapy. At screening, lesions at all disease sites were categorized as either measurable or nonmeasurable. Indicator lesions were selected and monitored throughout the trial using the same techniques and by the same person, whenever possible. Tumor response was evaluated according to the new Response Evaluation Criteria in Solid Tumors.[18]

Pharmacokinetics

Patients who completed at least one cycle of BAY 43-9006 treatment and had no missing pharmacokinetic measurements were valid for the pharmacokinetic analysis. Blood samples (5-mL aliquots) for the determination of plasma concentrations of BAY 43-9006 were collected during the first and second administration of the drug in each respective dose level before dosing (0 hour) and up to 96 hours after dosing in weeks 1 and 2.

Two liquid chromatograph/mass spectrometer/mass spectrometer methods had been developed for the determination of BAY 43-9006 concentrations in plasma with limits of quantifications of 0.1 mg/L or 0.001 mg/L. Both assay methods were applied in this study for the determination of the pharmacokinetic characteristics of BAY 43-9006. Mean interassay precision and accuracy, as determined by analysis of quality control samples, ranged from 0.3% to 10.4% and from 92.3% to 103.7%, respectively, considering all methods used.

Plasma pharmacokinetic parameters, area under the curve (AUC), maximum concentration (C_{max}), time to maximum concentration (t_{max}), and elimination half-life ($t_{1/2}$) for BAY 43-9006 were calculated using noncompartmental methods by KINCALC (a program developed by Bayer; Wuppertal, Germany). The linear-logarithmic trapezoidal method was used to calculate AUC, and apparent $t_{1/2}$ was calculated by linear least squares regression after logarithmic transformation of the terminal concentrations. Pharmacokinetic parameters were analyzed using descriptive statistics. Plasma concentration–time courses of BAY 43-9006 (calculated if two thirds or more of individual values were greater than the limits of quantifications) are presented as geometric mean values.

Pharmacodynamic Assay for Raf Kinase Inhibition by Flow Cytometry

The effect of BAY 43-9006 treatment on inhibition of Raf kinase was calculated by measuring inhibition of ERK phosphorylation in patients' PBLs following activation with phorbol myristate acetate.

Peripheral blood samples using EDTA as the anticoagulant were taken on day 0 (before treatment), on day 2, on day 7, and weekly thereafter for at least 6 weeks. Blood samples were always taken between 11:00 am and 1:00 pm.

T lymphocytes were isolated from the PBLs and were fixed and stained for MAPK activity using an antibody for p44/42 MAPK, an fluorescein isothiocyanate–goat-antirabbit antibody and an anti-CD7 antibody. Cells were resuspended in 1 mL phosphate-buffered saline and flow cytometry was performed under standard conditions following the assay protocol described by Chow et al.[19]

RESULTS

Patient Demographics

Sixty-nine patients with advanced, refractory solid tumors were recruited between July 2000 and February 2003. Patients' characteristics are listed in Table 1. All patients had measurable disease at baseline; the majority had been treated with surgery (93%) and/or systemic therapy (97%). The most common cancers were colorectal cancer (28 patients, 41%), hepatocellular carcinoma (HCC; nine patients, 13%), and breast cancer (four patients, 6%). Liver metastases were detected at baseline in 20 patients (29%). Six patients discontinued treatment during the initial 4-week treatment period, mostly due to progressive disease (n = 4). One patient withdrew consent, and another patient in the 100 mg bid cohort discontinued study treatment because of DLT (grade 3 diarrhea). All 69 patients were assessable for safety and treatment-emergent AEs were recorded.

Dose Escalation and MTD

DLTs were not observed for any patient on a noncontinuous dosing schedule. On the continuous dosing

Table 1. Patients' Characteristics

Characteristic	No. of Patients	%
Total No.	69	
Age, years		
Median		60
Range		18-75
Sex, male:female	44:25	
ECOG performance status		
0	26	38
1	36	52
2	7	10
Previous therapy		
Surgery	64	93
Systemic therapy	67	97
Radiotherapy	22	32
Tumor types by area		
Colon	28	41
Ovary	1	1
Breast	4	6
Liver (HCC)	9	13
Pancreas	1	1
Kidney	1	1
GI (other)	13	19
Skin	1	1
Other	11	15

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; GI, gastrointestinal.

Table 2. Treatment-Related Adverse Events

Adverse Event	No. of Patients	%	Worst Common Toxicity Criteria Grade 1		2		3	
			No. of Patients	%	No. of Patients	%	No. of Patients	%
Fatigue	27	39	16	23	7	10	4	6
Diarrhea	38	55	15	22	17	25	6	9
Hand-foot syndrome	16	23	6	9	6	9	4	6
Rash	18	26	11	16	7	10	0	0
Alopecia	11	16	6	9	3	4	2	3
Anorexia	29	42	28	41	1	1	0	0
Other skin reactions	5	7	5	7	0	0	0	0
Nausea	21	30	18	26	3	4	0	0
Stomatitis	5	7	2	3	3	4	0	0
Pancreatitis	3	4	0	0	0	0	3	4
Bilirubin	3	4	0	0	0	0	3	4

schedule (100 to 400 mg bid), one patient each in the 100 mg bid and 200 mg bid cohorts experienced a DLT (grade 3 pancreatitis and grade 3 diarrhea, respectively). At the 800-mg dose, two of six patients reported DLTs of grade 3 diarrhea, and one additional patient showed grade 3 fatigue. Because the prior dose level of 400 mg bid was not associated with significant toxicity, an intermediate dose of 600 mg bid BAY 43-9006 was investigated. At this dose, four of 14 patients (29%) experienced at least one dose-limiting skin toxicity during the initial 5-week treatment/observation period; therefore, 400 mg bid BAY 43-9006 was established as the MTD and the recommended dose for future studies.

Safety

In total, 75% of patients experienced treatment-related AEs (Table 2), which were unrelated to dosing schedule. The most frequent were gastrointestinal (61%) and dermatologic (41%) in nature.

Diarrhea was the most common gastrointestinal AE (55%) and was mostly mild to moderate in severity, although it was dose limiting (grade 3) in two of six patients receiving 800 mg bid continuous dosing, and in four patients across the other dose levels. ln all cases, diarrhea resolved within 24 to 48 hours of drug withdrawal. In general, grade 1 and 2 diarrhea did not require withdrawal of BAY 43-9006, and was easily managed with oral loperamide.

Three patients experienced grade 3 pancreatitis, which did not appear to be dose dependent: two patients on the 100 mg bid continuous BAY 43-9006 dosing schedule (3 weeks and 6 weeks, respectively, of therapy before the occurrence of pancreatitis), and one patient experienced pancreatitis after receiving 400 mg bid continuous BAY 43-9006 for 8 months. Upon withdrawal of the drug, all patients recovered within 10 to 14 days.

Transient grade 3 elevation of conjugated bilirubin, without concomitant elevation of other hepatic enzymes, was reported in three patients. None of these patients experienced additional pancreatitis, indicating different pathogenic mechanisms. Elevation of bilirubin appeared independently of the dose level and occurred on day 3 after the first application and resolved spontaneously by day 5. Mild to moderate stomatitis occurred in five patients, all of whom had concomitant oral candidiasis.

The most frequently observed dermatologic AEs were hand-foot syndromes (23%) and rash (26%). At the highest dose level (800 mg bid continuous), skin toxicity was mild to moderate (grade 2 in one out of six patients). In contrast, at 600 mg bid BAY 43-9006 continuous dose, skin toxicity was reported in nine of 14 patients, and was dose limiting in four of these patients. Skin toxicity occurred concomitantly with grade 1/2 diarrhea in five patients at this dose level. All other skin reactions, such as rash, were mild to moderate in severity. Significant (grade 3) alopecia occurred in two patients at dose level 400 mg bid continuous.

Dose-limiting fatigue was reported in four patients across all dose levels. In three patients, fatigue was associated with tumor progression. Nausea was also associated with tumor progression in all cases and showed no dose relationship. There were no hematologic, renal, or other AEs commonly associated with cytotoxic agents.

Table 3 shows the number of patients enrolled in each dosing schedule and the duration of therapy for each

Table 3. Treatment Summary by Treatment Group and Dose Level (all patients valid for safety analysis, n = 69)

Treatment Group	No. of Patients	Duration (days) Mean	Range
All noncontinuous dose levels	22	90.8	20-407
Continuous dosing, mg bid			
100	5	54.2	9-97
200	6	264	71-412
400	15	230	28-738
600	14	89.3	12-295
800	7	88.4	35-190

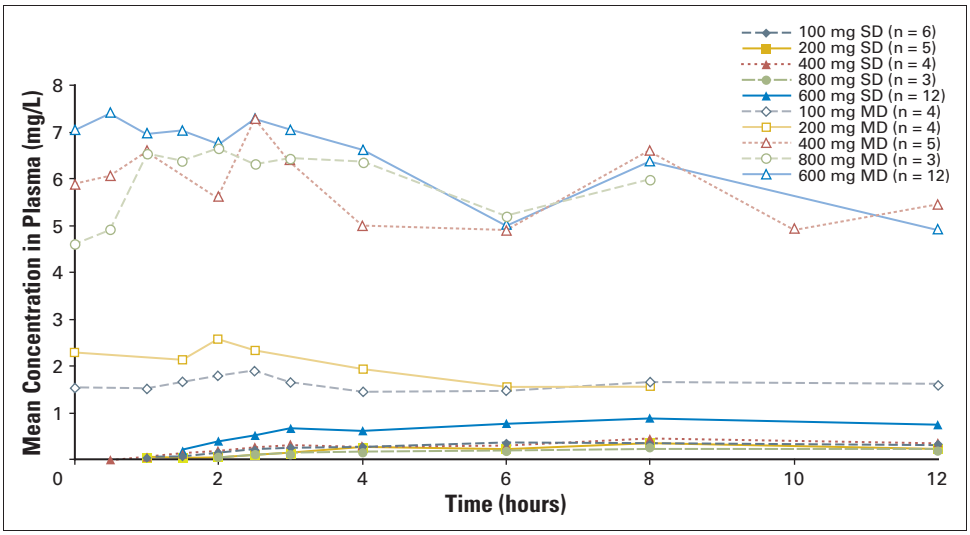

Fig 1. Mean plasma concentrations of BAY 43-9006 after single (SD) and multiple doses (MD) of 100, 200, 400, 600, or 800-mg BAY 43-9006 bid continuous dosing.

cohort. All patients treated on dose levels lower than 100 mg bid continuous dosing have been summarized as noncontinuous dosing levels. Regarding dose levels 600 mg bid and 800 mg bid, respectively, a considerable number of patients went off study due to toxicity.

Pharmacokinetics

A total of 60 patients were eligible for pharmacokinetic analysis; nine patients were excluded because of changes in drug administration schedules. BAY 43-9006 was absorbed at a moderate rate after the first dose, and C_{max} occurred at 2.5 to 12.5 hours after administration. Subsequently, plasma concentrations of BAY 43-9006 decreased slowly, and one or more peaks were frequently observed (Fig 1). There was no observable dose dependency in the plasma concentration-time profiles after the first dose of 100 to 800 mg BAY 43-9006 (Fig 2). Substantial accumulation in plasma following multiple bid administrations was observed.

AUC and C_{max} values were highly variable following single oral doses of BAY 43-9006 (Table 4). Increasing the dose of BAY 43-9006 from 100 to 400 mg did not result in a clear dose-response relationship for these parameters. Intake of food before dosing had no relevant impact on the pharmacokinetics of BAY 43-9006 except for slightly prolonging t_{max} (Table 4). Mean $t_{½}$ ranged from 24 to 38 hours.

Similar to the values observed after single dosing, AUC and C_{max} values were highly variable following multiple doses of BAY 43-9006 bid. Mean $AUC_{0–12}$ was lowest after 200 mg bid (Table 5). Maximum mean $AUC_{0–12}$ values were obtained at 600 mg bid, although the difference between 400 and 600 mg bid was only marginal. Further increasing the dose to 800 mg bid did not result in increased $AUC_{0–12}$ and C_{max} values (Fig 3).

Pharmacodynamic Assay for Raf Kinase Inhibition

Partial inhibition of PMA-stimulated ERK phosphorylation in PBLs was observed at 200 mg bid continuous dosing (data not shown). However, at dose level 400 mg bid almost complete inhibition of PMA-stimulated ERK

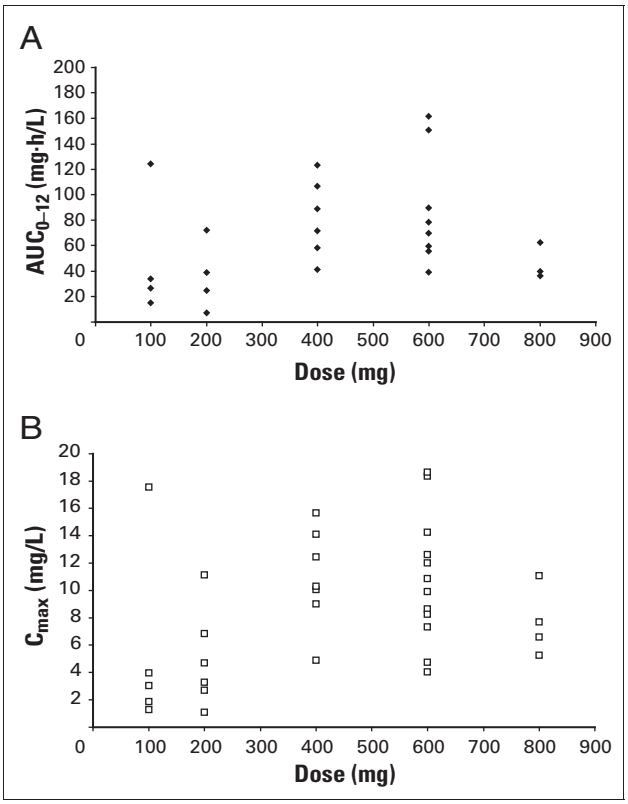

Fig 2. (A) Individual area under the curve ($AUC_{0–12}$) and (B) maximum concentration (C_{max}) values of BAY 43-9006 after multiple oral doses of BAY 43-9006 bid. Only patients on continuous dosing levels are included.

Table 4. Pharmacokinetic Parameters of BAY 43-9006 Following Single Oral Doses of 100 to 400 mg

		AUC (mg*h/L)		C_{max} (mg/L)		t_{max} (hours)		$t_{½}$ (hours)	
Dose (mg)	n	Geometric Means	% CV	Geometric Means	% CV	Median	Range	Geometric Means	% CV
100									
Fasting	3	83.8	18	2.69	39	3.4	2.6-8.1	28.9	20
Fed	3	49.8	58	1.98	69	7.9	3.0-8.2	37.9	2
200									
Fasting	3	31.9	12	1.08	7	2.1	1.5-2.5	29.5	77
Fed	3	47.6	41	1.52	82	4.3	2.7-6.2	31.8	36
400									
Fasting	3	107	15	3.42	13	2.5	1.5-2.6	23.8	5
Fed	3	82.3	18	2.44	26	6.0	1.0-12.1	28.1	26

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; t_{max}, time to maximum concentration; $t_{1/2}$, elimination half-life; CV, coefficient variation.

phosphorylation was observed on day 21 of a continuous dosing schedule (Fig 3). Similar results were obtained at 600 mg and 800 mg bid continuous dosing (data not shown).

Tumor Response

Sixty-six patients were evaluated for tumor response. Preliminary antitumor activity was analyzed only for patients treated continuously with BAY 43-9006 at doses of $\geq$ 100 mg bid (n = 45).

One patient, a 26-year-old male with HCC and a pelvic mass, showed a PR at 400 mg bid continuous BAY 43-9006, which lasted $>$ 6 months. A total of eight patients (18%) experienced disease stabilization lasting $>$ 6 months; in five of these patients (11%), stabilization lasted $>$ 12 months (Table 6). One heavily pretreated renal cell carcinoma (RCC) patient (three prior regimens) showed disease stabilization for almost 2 years. Half of the HCC patients experienced disease stabilization for at least 6 months; one patient is still being followed up. Although the results indicate a greater likelihood of antitumor activity with BAY 43-9006 at doses of $>$ 200 mg bid continuous, no obvious dose-response relationship could be deduced from the data.

DISCUSSION

The results of this phase I trial show that oral BAY 43-9006 administered daily was generally well tolerated by patients with advanced refractory solid tumors. Drug-related toxicities were mostly mild to moderate in severity and unrelated to the dosing schedule. The most common drug-related toxicities were of a gastrointestinal or dermatologic nature. Diarrhea was the most common gastrointestinal toxicity and appeared to be dose limiting in patients receiving the highest dose (800 mg bid continuous). Skin toxicity was dose limiting and occurred with mild diarrhea at 600 mg bid continuous BAY 43-9006. Based on the results of this study the MTD for BAY 43-9006 was 400 mg bid.

The pharmacokinetics of BAY 43-9006 exhibited a large interindividual variability after both single and multiple dosing. BAY 43-9006 is absorbed relatively slowly after oral administration as tablet formulation, probably due to slow dissolution in the gastrointestinal tract. In addition, preliminary data indicate that BAY 43-9006 is subjected to enterohepatic circulation, the extent of which may vary in different patients. Both processes may contribute to the observed intersubject variability of the pharmacokinetics. This variability, in combination with a low number of patients per cohort, may be the reason for the lack of a clear dose dependency of C_{max} and AUC of BAY 43-9006. No dose dependence of the extent of metabolism and of the metabolic formation rates was observed for this compound. The metabolism of BAY 43-9006 does therefore not contribute to the nonlinearity of the pharmacokinetics of this drug. The pharmacokinetic findings for

Table 5. Pharmacokinetic Parameters of BAY 43-9006 Following Multiple Oral Doses of 100 to 800 mg bid

		AUC_{0-12} (mg*h/L)		C_{max} (mg/L)		t_{max} (hours)	
Dose (mg)	n	Geometric Means	% CV	Geometric Means	% CV	Median	Range
100	3	23.8	43	2.31	54*	5.2	1.6–12.0*
200	3	16.1	83	2.84	88*	2.0	0–4.0*
400	5	71.7	43	9.35	44	3.0	0–12.0
600	8	79.0	52	9.81	51†	2.5	0–8.5†
800	3	44.9	30	7.21	28‡	2.1	1.0–6.5‡

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; t_{max}, time to maximum concentration; CV, coefficient variation.
*n = 4.
†n = 12.
‡n = 5.

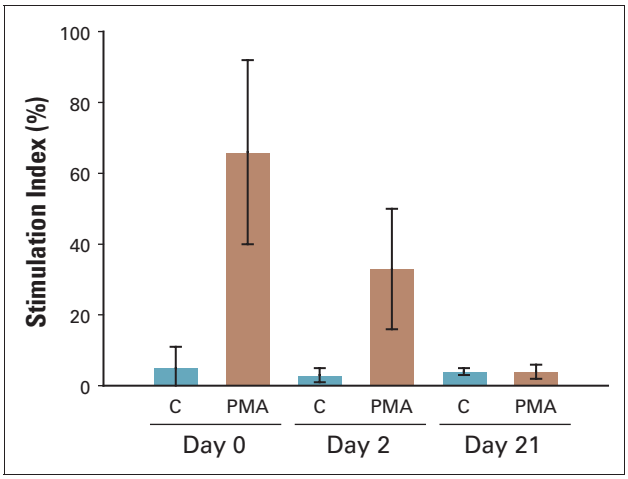

Fig 3. Flow cytometry results showing almost complete inhibition of phorbol myristate acetate (PMA) –induced ERK-phosphorylation (PMA 80 nmol/L final concentration) in patients' peripheral blood lymphocytes (PBLs). Results were shown only for patients (n = 6) treated with 400 mg bid continuous dosing. ERK phosphorylation in patients' PBLs without PMA stimulation is shown in columns labeled C (control). Stimulation index is defined as: number of CD7-positive cells + ERK-phosphorylated cells × 100/ number of CD7-positive cells ± ERK-phosphorylated cells. Therefore, the stimulation index reflects the percentage of cells with activated ERK among all CD7-positive cells. Data are shown at screening (day 0 before first BAY 43-9006 application), on day 2, and after treatment for more than 20 days. Above each column, mean stimulation index ± standard deviation is given.

BAY 43-9006 reported here are consistent with those obtained in an additional phase I study (unpublished data). BAY 43-9006 was absorbed at a moderate rate after the first dose. Intake of food before dosing had no relevant impact on the pharmacokinetic profile of BAY 43-9006 (data not shown). Mean terminal $t_{½}$ ranged from approximately 24 to 38 hours. The pharmacodynamic results provided a proof-of-concept; that is, clinically available BAY 43-9006 plasma concentrations at the recommended dose for further phase II testing are sufficient for inhibition of cellular signaling, including ERK-phosphorylation, at least in PBLs. Due to circadian variability of MAPK activation in PBLs (data not shown), the time point of blood sampling is critical. Pharmacodynamic variability was significantly lower than pharmacokinetic variability. Since pharmacodynamic measurements were not performed in tumor samples and antitumor efficacy was not the primary objective of this study, further biomarker studies are necessary in phase II studies to allow conclusions on clinical usefulness.

Preliminary efficacy data from this study suggest that BAY 43-9006 is associated with clinically meaningful and durable stabilization of progressive disease, rather than tumor regressions. One confirmed PR was observed in a patient with HCC, and prolonged SD was reported in eight patients (18%), three with HCC. In addition, one RCC patient had SD for almost 2 years. Tannapfel et al[20] recently reported that B-Raf mutations were rare in HCC patients. However, activation of the Ras/Raf/MEK1/2 pathway may play an important role in hepatocellular carcinogenesis.[21] The VEGF family is also essential in the pathogenesis and prognosis of vascular tumors such as HCC and RCC, and bevacizumab, an antiangiogenesis inhibitor targeted against VEGF, has demonstrated significant prolongation in time to disease progression in trials of patients with metastatic RCC.[22] An agent such as BAY 43-9006, which targets both the Raf/MEK/ERK pathway and VEGFR, may hold promise in the treatment of solid tumors such as RCC.

In conclusion, BAY 43-9006 is a novel dual-action Raf kinase and VEGFR inhibitor, which is orally available and has a favorable safety profile in patients with advanced solid tumors. This, together with the antitumor activity observed after treatment with BAY 43-9006, provides a rationale for further evaluation in patients with advanced cancer. The recommended dose of BAY 43-9006 for future studies is 400 mg bid as a continuous dosing schedule.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Employment: Erich Brendel, Bayer Healthcare; Claus G. Haase, Bayer Healthcare; Brian

Table 6. Best Response by Tumor Type Including Only Patients Treated Continuously With BAY 43-9006 ≥ 100 mg bid, and Overall Response According to RECIST (n = 45)

Primary Tumor Site	No. of Patients	Duration (days)		Medication (days)		Best Response					Disease Stabilization	
		Median	Range	Median	Range	PR	NC	PD Clin	PD Meas	NA	> 6 months	> 1 year
Colorectal	26	94.0	28-412	86.5	28-405		14	1	11		4	2
HCC	6	193.5	35-428	187	5-386	1	4		1		2	1
RCC	1	738		680			1				0	1
NSCLC	1	307		301			1				1	0
Other	11	65	22-638	59	22-638		5		5	1	1	1
Total	45	83	22-738	79	22-680	1 (2%)	25 (56%)	1 (2%)	17 (38%)	1 (2)	8 (18%)	5 (11%)

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; PR, partial response; NC, no change; PD Clin, progressive disease, clinical judgment; PD Meas, progressive disease, measurement proven; NA, not assessable for response; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; NSCLC, non–small-cell lung cancer.

Schwartz, Bayer Pharma Corp West. Consultant/Advisory Role: Dirk Strumberg, Bayer AG, Onyx Pharma. Honoraria: Dirk Strumberg, Bayer AG, Onyx Pharma. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue.

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