Safety and Pharmacokinetics of the Dual Action 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, a novel multikinase inhibitor, prevents tumor growth by combining two antitumor activities: inhibition of both tumor cell proliferation and tumor angiogenesis. This phase I, open-label, nonrandomized, noncontrolled, single-arm, dose escalation study was done to determine the maximum tolerated dose (MTD), safety profile, pharmacokinetic variables, effect on biomarkers, and tumor response with BAY 43-9006 in 19 patients with advanced, refractory solid tumors.

Experimental Design: BAY 43-9006 was given orally in repeated cycles of 1-week on/1-week off. The study comprised five dose levels, ranging from 100 mg twice daily (bid) to 800 mg bid. Treatment of each patient continued until unacceptable toxicity, tumor progression, or death.

Results: Rash and hypertension were the dose-limiting toxicities at the 800 mg bid dose requiring study drug discontinuation; therefore, the MTD of BAY 43-9006 in this study was determined to be 600 mg bid. BAY 43-9006 was generally well tolerated, with mild to moderate toxicities. Pharmacokinetic analysis showed early absorption followed by delayed secondary peaks and slow terminal elimination. Stable disease was achieved in five patients: one patient showed reduced tumor activity (positron emission tomography scan) and reduced mitogen-activated protein kinase signaling (lower phospho-ERK); one patient remained on treatment until study end point.

Conclusions: The results confirm the favorable safety profile of BAY 43-9006 and support the development of this compound for the treatment of solid tumors.

Many molecular pathways, including cell cycle control pathways and the complex processes of angiogenesis and metastasis, mediate tumor growth and progression. Thus, chemical mediators involved in these signaling pathways are potential targets for anticancer treatments. Ras signaling mediates cellular proliferation, differentiation, and transformation by relaying extracellular signals to cytoplasmic effector molecules via a number of signaling cascades, the best characterized of which is the Raf/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway (1). Activation mutations in *ras* are prevalent in solid tumor malignancies and are found in 30% to 50% of colon carcinomas, 30% of lung carcinomas, and 70% to 90% of pancreatic carcinomas (2). Ras activation can be induced by activation of receptor tyrosine kinases, such as the vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (3–5).

BAY 43-9006 is a novel kinase inhibitor, which has been shown in preclinical models to have activity against several kinases, including C-Raf, B-Raf, VEGFR-2, platelet-derived growth factor receptor-β, CKIT, and FLT3 kinase (6). Thus, it has the potential to prevent tumor growth by combining two anticancer activities: inhibition of both tumor cell proliferation and tumor angiogenesis. BAY 43-9006 has shown significant dose-dependent antitumor activity in preclinical models of different human tumor types, including colon, pancreatic, lung, breast, and ovarian carcinomas, and this activity was correlated with inhibition of the Raf/MEK/ERK pathway (6–10). This antitumor activity was observed in cancers with *ras* mutations, as well as those in which Ras is activated through activation of growth factor receptors and in those with mutations in *B-raf* (9).

In addition to inhibiting tumor cell proliferation, BAY 43-9006 has also been shown preclinically to exert an antiangiogenic effect by targeting the receptor tyrosine kinases VEGFR-2 and platelet-derived growth factor receptor and their associated signaling cascades (6). The dual pharmacologic effect of BAY 43-9006 suggests that this compound could potentially be effective in a wide range of cancers, especially those in which tumors are well vascularized.

The pharmacokinetic profile of orally given BAY 43-9006 is being investigated in a number of *in vitro* and *in vivo* studies, most of which are ongoing. BAY 43-9006 accounted for 73% of

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exposure circulating in plasma, whereas 17% was the M2 metabolite. Other minor metabolites accounted for <1% of circulating radioactivity in plasma. Although BAY 43-9006 and its metabolites have similar pharmacologic activity, these data suggest that the metabolites are not present in the plasma at a significantly high concentration. Therefore, BAY 43-9006 does not seem to have major active metabolites circulating in plasma.[4] Ongoing studies show that BAY 43-9006 is 99.5% bound to plasma proteins and that the bioavailability of BAY 43-9006 following administration of a moderate fat meal was similar to that when given in the fasted state. BAY 43-9006 absorption was reduced by 30% when given with a high-fat meal.[4]

In vitro data suggest that BAY 43-9006 undergoes oxidative metabolism by the cytochrome *P*450 (CYP) enzyme system, especially by CYP3A4, and therefore has a potential for CYP-mediated drug-drug interaction. However, coadministration of the CYP3A inhibitor ketoconazole in healthy volunteers had no effect on the pharmacokinetics of BAY 43-9006.[4] Although the formation of the main circulating metabolite of BAY 43-9006, the N-oxide, was decreased by ketoconazole, this did not result in an increase in concentrations of the parent compound. This suggests that other metabolic pathways (i.e., glucuronidation; see below), play a major role in BAY 43-9006 metabolism. Preliminary phase I findings also suggest that there is no pharmacokinetic interaction with standard chemotherapeutics such as gemcitabine or oxaliplatin, whereas there seems a 21% increase in doxorubicin AUC when cogiven with BAY 43-9006. The clinical significance of this increase is being investigated. Furthermore, there seems no relationship between BAY 43-9006 pharmacokinetics and age, gender, body weight, and hepatic function (serum bilirubin) or renal (serum creatinine) function. Therefore, although this needs to be confirmed, the dose of BAY 43-9006 may not have to be adjusted in patients with hepatic or renal impairment. Following oral administration of the [^{14}C]-labeled BAY 43-9006 to healthy volunteers, ~77% of the given dose was found in the feces (51% was unchanged) whereas 19% was excreted mainly in the glucuronide form in urine.[4] Glucuronidation indicates that BAY 43-9006 is metabolized by enzymes other than CYP.

Preclinical data suggest that the anticancer activity of BAY 43-9006 may be cytostatic, requiring continued exposure to the drug for growth inhibition: tumor growth seems suspended while the drug is present and returns to baseline rates when the agent is withdrawn. Therefore, a balance needs to be achieved between minimizing the period off drug and avoiding the potential toxicity associated with extended exposure. The primary objective of this phase I study was to determine the maximum tolerated dose (MTD) of BAY 43-9006 given orally on a twice-daily (bid) schedule in repeated cycles of 7-day on/7-day off treatment. The secondary objectives were to define the pharmacokinetic variables, to examine the effect of biomarkers and to study tumor response in patients with advanced, refractory solid tumors.

Patients and Methods

Patient selection. Patients ages ≥18 years were eligible for enrollment in this study if they had documented evidence of incurable, advanced, metastatic, or recurrent solid tumors that are refractory to available therapy. Additional enrollment criteria included Eastern Cooperative Oncology Group performance status of 0, 1, or 2; life expectancy of at least 12 weeks; and adequate bone marrow (hemoglobin >9.0 g/d, neutrophils >1,500/mm^3, platelets >75 000/mm^3), hepatic (bilirubin <1.5 × upper limit of normal, alanine aminotransferase, and aspartate aminotransferase <2.5 × upper limit of normal), and renal (serum creatinine <1.5 × upper limit of normal) function. All patients gave written informed consent. Patients were eligible if they had received prior adjuvant chemotherapy, or had up to three prior chemotherapy regimens for metastatic disease.

Exclusion criteria included the following: treatment within 4 weeks of study entry with other chemotherapy or immunotherapy; radiotherapy within 3 weeks of study entry; biological response modifiers within 3 weeks of study entry; bone marrow transplant or stem cell rescue within 4 months of study entry; investigational drug therapy within 4 weeks of study entry; use of ketoconazole, itraconazole, ritonavir, or grapefruit juice; previous exposure to Ras pathway inhibitors; pregnant or lactating women; or substance abuse. Individuals who had any of the following medical conditions were also excluded: clinically evident congestive heart failure; serious cardiac arrhythmias; symptoms of coronary heart disease or ischemia on a cardiac stress test, present either at screening or by history; history of HIV, or chronic hepatitis B or C; active infections; brain metastases; history of seizure disorder; or history of organ allograft.

Treatment plan. This phase I, open-label, non–placebo-controlled, dose escalation study was conducted at two sites in the United States (Dana-Farber Cancer Institute, Brigham and Women's Hospital and Massachusetts General Hospital Cancer Center, Boston, MA and University of Southern California/Kenneth Norris Comprehensive Cancer Center, Los Angeles, CA) between October 2001 and February 2003. Treatment continued until unacceptable toxicity, tumor progression, or death.

Five dose levels (groups) were investigated in the study: 100, 200, 400, 600, and 800 mg bid, given orally in repeated 2-week cycles: 1-week on/1-week off treatment. The conservative starting dose of 100 mg bid BAY 43-9006 was chosen because it was within the predicted therapeutic range but was not excessively toxic based on previous phase I experience with different dosing schedules (11). Subsequent groups were treated according to a standardized dose escalation scheme, depending on the worst toxicity experienced by patients enrolled at the prior dose level, and the clinical significance of that toxicity. Toxicity was evaluated and graded according to the National Cancer Institute Common Toxicity Criteria version 2.0 (12). Dose-limiting toxicity (DLT) was defined as grade ≥4 hematologic toxicity for >5 days, or grade ≥3 nonhematologic toxicity. Three patients were initially enrolled into each dosing group. If no DLTs were observed, the dose escalation was employed and three patients were enrolled at the next dose. If any patient developed DLT, three additional patients were enrolled at that dose level. If two of these additional patients experienced DLT, dose escalation was stopped and the previous dose was determined as the MTD for BAY 43-9006. Up to 10 patients could be enrolled at the declared MTD to obtain additional safety data at the recommended dose.

Patient evaluation. Tumor measurements were taken at baseline (within 4 weeks before the start of treatment), and subsequent measurements were obtained every 6 weeks for comparison. Guidelines from the Response Evaluation Criteria in Solid Tumors committee were used to evaluate tumor response and progression. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions were used in Response Evaluation Criteria in Solid Tumors (13).

Baseline measurements of a maximum of 10 lesions identified as target lesions were recorded. These 10 lesions, which were representative of all involved organs, were selected on the basis of their size and their suitability for accurate repetitive measurements. The objective tumor response was characterized using the baseline sum of longest diameters for all target lesions. Measurements were not made for nontarget lesions, but these were noted at baseline and followed as "present" or "absent."

[4] Unpublished data.

The best response of each patient was classified according to the following criteria. Complete response was defined as the disappearance of all clinical and radiological evidence of tumor (both target and nontarget). A 30% decrease in the sum of longest diameters of target lesions (taking as reference the baseline sum of longest diameters) was classified as a partial response. Stable disease was defined as disease that had a <30% decrease or <20% increase in the sum of longest diameters. An increase of ≥20% in the sum of longest diameters of measured lesions (taking as references the smallest sum of longest diameters recorded since the treatment started), or appearance of any new lesion, were characterized as progressive disease. Unequivocal progression of a nonmeasured lesion was also evidence of disease progression. The duration of response was defined as the time period from the initial measurement of complete/partial response (whichever was first recorded) to the first date that recurrent disease or progressive disease was objectively documented. Duration of stable disease was measured from the start of therapy until the criteria for progression were met. The same method of assessment and the same techniques were used to characterize each identified and reported lesion at baseline and during follow-up.

Safety. Safety variables included results of medical history; physical examination; assessment of vital signs; and incidence of adverse events (patient-reported complaints), DLTs, and abnormal laboratory values.

Pharmacokinetics. Blood samples (5 mL) were collected on day 1 of the first cycle at 0 (predose), 0.5, 1, 2, 6, 10 to 12, and 24 hours after drug administration. Additional blood samples were collected on day 7 of cycle 1 and subsequent cycles (cycles 2 and 4) at 48, 72, 96, and 168 hours later. Plasma was removed from the blood samples by centrifugation and stored at −70°C. Plasma samples were analyzed for BAY 43-9006 using a validated liquid chromatograph tandem mass spectrometer assay with a lower limit of quantification of 0.01 μg/mL. Based on quality control samples of 0.01 to 16 mg/L that were assayed along with study samples, mean interassay precision ranged from 1.3% to 4.7%, and mean accuracy ranged from 92% to 103%.

Pharmacokinetic variables measured were area under the plasma concentration-time curve from 0 to 12 hours ($AUC_{0\text{-}12}$), maximum plasma concentration (C_{max}), time to maximum concentration (t_{max}), and elimination half-life ($t_{1/2}$). Plasma concentration-time data were evaluated by noncompartmental methods using WinNolin 4.0. 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.

Biomarker evaluation. Expression levels of the biomarker phospho-ERK (pERK) were detected in tissue sections using immunohistochemical staining with a polyclonal rabbit antibody that detects the phosphorylation status of the p44 and p42 mitogen-activated protein kinases (Erk1 and Erk2; Cell Signaling Technologies, Inc., Beverly, MA). This polyclonal antibody was shown to mediate equivalent levels of staining as a monoclonal antibody against pERK. All sections were evaluated qualitatively and semiquantitatively. Semiquantitative evaluation of antigen expression was based on the percentage of antigen expression throughout the entire specimen as follows: 0% to 5% = positive antigen expression ≤5%; 6% to 25% = first quartile (1Q); 26% to 50% = second quartile (2Q); 51% to 75% = third quartile (3Q); 76% to 100% = fourth quartile (4Q).

Statistics. No formal sample size estimation was done because this was primarily a descriptive safety and tolerability study. Summary statistics are presented for demographic and biomarker variables. For safety assessments, patients who received at least one dose of BAY 43-9006 and had posttreatment data available were evaluated. An intention-to-treat population, which included all patients with at least one assessment after the start of BAY 43-9006 treatment, was used for assessment of time to death, time to relapse, and response rate.

Results

Patients' characteristics. A total of 19 patients were enrolled in this study, all of whom received BAY 43-9006 and were valid for pharmacokinetic and safety analyses. The dose levels assessed were as follows: three patients at 100 mg bid, three at 200 mg bid, four at 400 mg bid, six at 600 mg bid, and three at 800 mg bid. Patients' baseline characteristics are shown in Table 1. The most common primary cancer site was the colon (six patients, 32%) and the most common histology was adenocarcinoma (eight patients, 42%). The median time from diagnosis to the start of study treatment was 3.8 years (range, 0.8-11.2 years), and 17 patients (89%) had received prior anticancer therapy. Five patients (26%) had been treated previously with radiotherapy, and all 19 patients had received surgery before enrollment in this trial.

Dose escalation. The numbers of cycles of treatment received by patients are shown in Table 2. The maximum number of cycles received by any patient was 30 (100 mg bid group). Six (32%) patients received at least five cycles of treatment. The median and mean durations of treatment were 5.0 and 10.2 weeks (SD, 14.9), respectively. The minimum treatment duration was 1 week (800 mg bid group). The maximum treatment duration was 65 weeks (100 mg bid group). This patient subsequently continued to receive drug on an extension trial for approximately one further year before having disease progression.

Three dose interruptions occurred in three patients in three cycles. One patient in the 600 mg bid group erroneously took 11 (50 mg) tablets instead of 12 in cycle 1. A second patient

Table 1. Patients' baseline characteristics

Characteristics	
Gender, *n* (%)	
Male	11 (58)
Female	8 (42)
Race, *n* (%)	
Caucasian	17 (89)
Other	2 (11)
Mean age (y)	53.7
ECOG, *n* (%)	
0	6 (32)
1	9 (47)
2	4 (21)
Sites of disease	
1-3	13 (69)
≥4	6 (31)
Primary tumor site	
Colon	6 (32)
Sigmoid	2 (11)
Pancreas	2 (11)
Abdomen	2 (11)
Other/unknown	7 (35)
Median duration of disease (y)	3.8
Prior anticancer therapy regimens (including immunotherapy)	
1	5 (26)
2	2 (11)
3	5 (26)
≥4	5 (26)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Number of cycles per group

No. cycles	100 mg bid (*n* = 3)	200 mg bid (*n* = 3)	400 mg bid (*n* = 4)	600 mg bid (*n* = 6)	800 mg bid (*n* = 3)	Total (*N* = 19), *n* (%)
1					3	3 (16)
2	1	1	1	1		4 (21)
3	1		1	3		5 (26)
4		1				1 (5)
≥5	1	1	2	2		6 (32)
Median (minimum, maximum)	3 (2, 30)	4 (2, 10)	4 (2, 14)	3 (2, 7)	1 (1, 1)	3 (1, 30)

requested that a dose be withheld at cycle 16. A third patient had a dose interruption in cycle 2 due to toxicity (grade 4 fatigue and grade 4 depressed level of consciousness).

Of the 19 patients, 14 (74%) discontinued study treatment because of disease progression and four (21%) because of an adverse event. One patient at 600 mg bid had depressed level of consciousness, which was not related to BAY 43-9006, and three patients at 800 mg bid had rash/desquamation, which was related to BAY 43-9006. One patient in the 100 mg bid group continued treatment to the end of the study.

Maximum tolerated dose, safety profile, and dose-limiting toxicity. All 19 patients received at least one dose of study medication and were evaluable for safety analysis. There were six protocol-defined DLTs in five patients. Three of these DLTs occurred at the 800 mg bid dose level and required discontinuation from the study. Of these three DLTs, two patients had

Table 3. Incidence of all drug-related adverse events

Category	Grade	100 mg bid (*n* = 3), *n* (%)	200 mg bid (*n* = 3), *n* (%)	400 mg bid (*n* = 4), *n* (%)	600 mg bid (*n* = 6), *n* (%)	800 mg bid (*n* = 3), *n* (%)	Total (*N* = 19), *n* (%)
Any category	1 or 2*	2 (67)	0 (0)	2 (50)	3 (50)	0 (0)	7 (37)
	3	0 (0)	0 (0)	2 (50)	0 (0)	3 (100)	5 (26)
Blood/bone marrow (hemoglobin)	1 or 2*	0 (0)	0 (0)	1 (25)	1 (16.7)	0 (0)	2 (11)
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Flu-like symptoms (fatigue)	1 or 2*	0 (0)	0 (0)	0 (0)	0 (0)	2 (67)	2 (11)
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal							
Anorexia	1 or 2*	1 (33)	0 (0)	0 (0)	0 (0)	1 (33)	2 (11)
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea	1 or 2*	0 (0)	0 (0)	1 (25)	0 (0)	1 (33)	2 (11)
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Stomatitis/pharyngitis	1 or 2*	0 (0)	0 (0)	1 (25)	0 (0)	1 (33)	2 (11)
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	1 or 2*	1 (33)	0 (0)	1 (25)	0 (0)	0 (0)	2 (11)
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatic	1 or 2*	0 (0)	0 (0)	2 (50)[c d]	1 (17)[e]	0 (0)	3 (16)
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Metabolic	1 or 2*	0 (0)	0 (0)	2 (50)[f]	1 (17)[f]	0 (0)	3 (16)
	3	0 (0)	0 (0)	1 (25)[g]	0 (0)	0 (0)	1 (5)
Pulmonary (dyspnea)	1 or 2*	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	3	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	1 (5)
Skin							
Pruritis	1 or 2*	0 (0)	0 (0)	1 (25)	1 (17)	2 (67)	4 (21)
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Rash/desquamation	1 or 2*	0 (0)	0 (0)	2 (50)	1 (17)	1 (33)	4 (21)
	3	0 (0)	0 (0)	0 (0)	0 (0)	2 (67)	2 (11)

NOTE: No grade 4 drug-related adverse event was experienced by any patient from any group.
*Grade 1 or 2 adverse events in >10% of total number of patients.
[c]Hypoalbumemia, [d]alkaline phosphatase, [e]bilirubin, [f]hypocalcemia, [g]hyponatremia.

Table 4. Incidence of treatment-emergent grade 3 or 4 adverse events

Category	Grade	100 mg bid (*n* = 3), *n* (%)	200 mg bid (*n* = 3), *n* (%)	400 mg bid (*n* = 4), *n* (%)	600 mg bid (*n* = 6), *n* (%)	800 mg bid (*n* = 3), *n* (%)	Total (*n* = 19), *n* (%)
Any category	3	2 (67)	0 (0)	3 (75)	4 (67)	3 (100)	12 (63)
	4	0 (0)	1 (33)	1 (25)	0 (0)	0 (0)	2 (11)
Blood/bone marrow (hemoglobin)	3	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Cardiovascular							
Hypertension	3	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	1 (5)
Thrombosis/embolism	3	0 (0)	1 (33)	1 (25)	0 (0)	0 (0)	2 (11)
Edema	3	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Coagulation (prothrombin time)	3	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Flu-like symptoms							
Fatigue	3	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
	4	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Gastrointestinal							
Anorexia	3	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Ascites	3	0 (0)	0 (0)	0 (0)	2 (33)	0 (0)	2 (11)
Constipation	3	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (5)
Dehydration	3	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Diarrhea (patients with and without colostomy)	3	0 (0)	0 (0)	2 (50)	0 (0)	0 (0)	2 (11)
Nausea	3	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Vomiting	3	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Genitourinary							
Creatinine	3	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Ureteral obstruction	3	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (5)
Hepatic							
Hypoalbumenia	3	0 (0)	0 (0)	1 (25)	1 (17)	0 (0)	2 (11)
Alkaline phosphatase	3	1 (33)	0 (0)	1 (25)	2 (33)	0 (0)	4 (21)
Infection (without neutropenia)	3	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Musculoskeletal (muscle weakness)	3	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (5)
Metabolic							
Hypocalcemia	4	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	1 (5)
Hyponatremia	3	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Neurologic (depressed level of consciousness)	3	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (5)
	4	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Pain							
Abdominal cramping	3	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	1 (5)
Pleuritic pain	3	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Pulmonary							
Pleural effusion	3	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (5)
Hypoxia	3	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (5)
Dyspnea	3	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	1 (5)
Skin (rash/desquamation)	3	0 (0)	0 (0)	0 (0)	0 (0)	2 (67)	2 (11)

grade 3 rash/desquamation and one patient had grade 3 hypertension and a grade 2 rash. Therefore, the MTD for this dosing schedule was determined to be 600 mg bid BAY 43-9006.

The drug-related adverse events and most common adverse events are shown in Tables 3 and 4, respectively. Twelve patients reported at least one adverse event related to study medication (Table 3). There were no grade 4 events perceived to be drug related; however, two patients reported three grade 4 events thought to be disease related (fatigue, hypocalcemia, and altered mental status; Table 4). Twelve patients experienced grade 3 adverse events (Table 4). Pruritus and rash/desquamation were the most common drug-related adverse events, occurring in at least two patients per group (Table 3). The increases in pruritus and rash were dose dependent, increasing in severity and frequency at the 400 mg bid dose level and higher.

Pharmacokinetics. After administration of BAY 43-9006 tablets, the plasma concentration-time profile was characterized by a slow absorption phase. In some patients, a secondary peak was observed 6 to 8 hours after dosing. An exponential decay in mean plasma concentrations of BAY 43-9006 was generally observed 24 to 72 hours after the last dose on day 7 (Fig. 1A). The plasma concentrations observed in a representative individual patient after administration with 400 mg bid exhibit a similar profile (Fig. 1B). The mean pharmacokinetic variables after 7 days of dosing in cycle 1 are shown in Table 5.

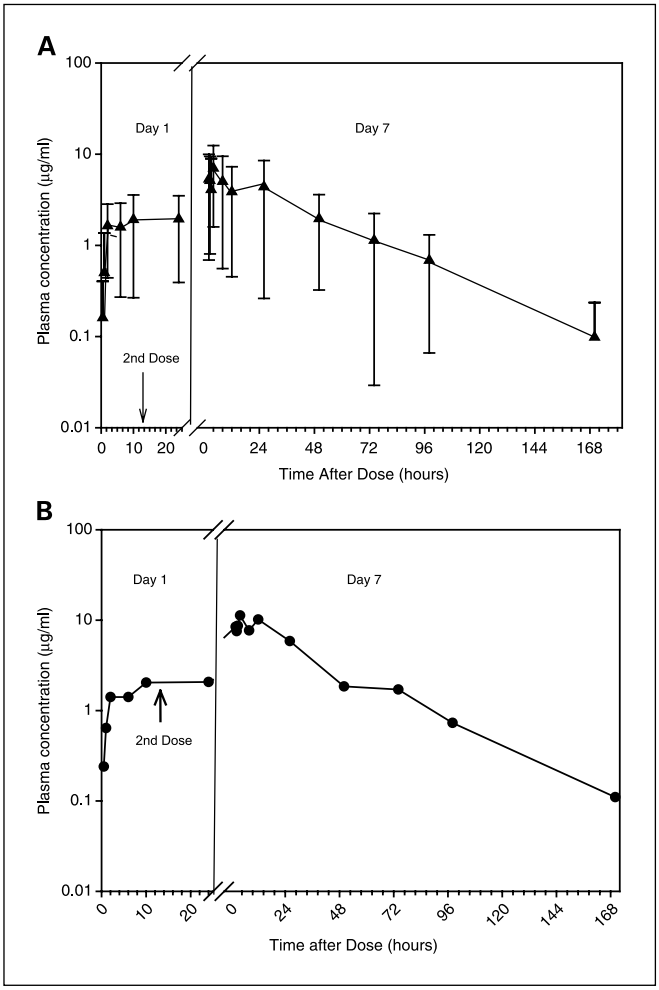

Fig. 1. *A*, plasma concentrations of BAY 43-9006 concentrations measured during the course of the study. *Points,* means; *bars,* SD. The negative error bar was not included in the final point as it was <0. *B*, concentrations on days 1 and 7 of cycle 1 after administration of 400 mg bid BAY 43-9006 to patient 2021.

There was significant interpatient variability in the pharmacokinetics of BAY 43-9006. C_{max} and AUC values of BAY 43-9006 increased less than proportionally with increasing dose. Furthermore, detailed pharmacokinetic analyses of BAY 43-9006 metabolites are ongoing.

BAY 43-9006 accumulated on multiple dosing, with mean C_{max} and $AUC_{0\text{-}12}$ values being significantly greater on day 7 compared with day 1. However, with the variability in $t_{1/2}$ (mean $t_{1/2}$ range, 20.0-38.1 hours) and the delayed secondary peaks in the plasma concentration-time profile occurring >6 hours after dosing, BAY 43-9006 exhibited variability in its accumulation. The mean BAY 43-9006 accumulation ratio for C_{max} at 400 mg bid was 3.8 and the mean accumulation ratio for AUC was 5.7.

No relationship between baseline demographics and BAY 43-9006 exposure was observed. Grade 3 and 4 drug-related adverse events were evaluated for their relationship with BAY 43-9006 dose, C_{max}, and $AUC_{0\text{-}12}$. At a given dose, there was no clear relationship among drug-related adverse events, dose, and BAY 43-9006 exposure.

Response to therapy. Twelve (63%) of the 19 patients showed signs of disease progression by initial radiological reimaging, five (26%) patients had stable disease, and no patients had an objective response. Two patients (11%) discontinued treatment with clinical evidence of worsening disease but without the final scan being done. The median time to disease progression was 42 days, and 75% of the patients showed signs of progressive disease by 84 days.

Although no objective responses were observed in this study, two patients had important findings of note. A 50-year-old male with metastatic melanoma involving the right thigh, liver, and lung was treated at the 600 mg bid dose level and had a minor response. Comparison of paired biopsy specimens taken from a melanoma on the right thigh on day 1 of cycle 1 and on day 7 of cycle 2 showed a decrease in the percentage of cell nuclei positively stained for pERK from the 4Q level (76-100%) to the 2Q level (26-50%; Fig. 2). In addition, positron emission tomography scans of the same tumor at baseline and day 22 showed a reduction in uptake of [^{18}F]2-fluoro-2-deoxy-D-glucose, suggesting a reduction in tumor activity induced by BAY 43-9006 treatment (Fig. 3). This was associated with a reduction in symptoms. Further scans at days 43 and 64 showed stable disease, but a new lesion was detected at day 85, and study treatment was discontinued due to disease progression.

A 70-year-old Caucasian man with metastatic renal cell carcinoma (RCC) with bony and mediastinal metastases commenced treatment with BAY 43-9006 100 mg bid in October 2001. At study end point, he remained on treatment with stable disease and was entered into a BAY 43-9006 extension trial. The patient had stable disease and continued therapy for a total of ~2 years before progressing.

Discussion

The results of this phase I trial show that BAY 43-9006 was generally well tolerated, with mild to moderate toxicities, and that the MTD of BAY 43-9006, when given orally for 1-week on/1-week off, is 600 mg bid.

BAY 43-9006 was evaluated in three other parallel phase I studies using different dosing schedules (continuous bid dosing, 21 days on drug/7 days off, and 28 days on/7 days off). The MTD in these other studies was 400 mg bid, with DLTs occurring more frequently at 600 mg bid and above (11). The higher MTD reached in the present study likely reflects the shorter duration of time on study treatment, which enabled patients to tolerate higher doses of BAY 43-9006 without the appearance of DLTs. Based on the combined results from all four phase I trials, the recommended phase II dose for BAY 43-9006 is 400 mg bid.

The pharmacokinetic profile established in this study is similar to that shown in the other phase I studies of BAY 43-9006 (11). BAY 43-9006 exhibited an early absorption phase followed by delayed secondary peaks. There was significant interpatient variability with BAY 43-9006. This may be explained in part by the small sample size. Data from this and other studies indicated no apparent relationship between drug-related toxicity and plasma concentrations of BAY 43-9006 at any given dose level. BAY 43-9006 accumulated on multiple dosing, consistent with its relatively long half-life. There was a less than proportional increase in the C_{max} and AUC values of BAY 43-9006.

Table 5. Mean plasma BAY 43-9006 pharmacokinetic variables after dosing for 7 d in cycle 1

Dose level (mg bid)	AUC0-12 (μg·h/mL), *n*		C_{max} (μg/mL), *n*		t_{max} (h), *n*		$t_{1/2}$ (h), *n*
	Geo mean (~CV%,)		Geo mean (~CV%,)		Median (range)		Geo mean (~CV%,)
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 7
100	1	3	3	3	3	3	3
	6.8 (NC)	24.4 (76.3)	1.0 (31.8)	3.5 (73.7)	6.0 (2.0-7.3)	2.0 (2.0-2.0)	38.1 (47.8)
200	1	3	3	3	3	3	3
	6.1 (NC)	19.1 (16.9)	0.8 (85.6)	2.6 (8.6)	6.0 (2.0-6.0)	2.0 (0.5-24.1)	20.1 (12.8)
400	2	4	4	4	4	4	3
	18.0 (5.3)	56.6 (90.5)	2.3 (37.3)	6.2 (106.7)	9.2 (2.0-12.0)	2.0 (0.0-6.0)	20.0 (21.9)
600	3	6	6	6	6	6	6
	21.0 (81.3)	64.8 (76.8)	2.7 (61.2)	6.6 (70.9)	6.0 (2.0-9.9)	1.5 (0.1-6.5)	24.3 (21.0)
800	2	3	3	3	3	3	3
	23.7 (14.7)	92.8 (32.4)	4.6 (7.4)	12.3 (32.8)	10.0 (2-12.0)	2.1 (1.0-24.0)	32.1 (34.7)

NOTE: ~CV% is the approximate coefficient of variation. AUC_{0-12} is the AUC value over the dosing interval, after 7 d of dosing, over a nominal period of 12 h (the exact time interval may be different for each patient). For t_{max}, the median, instead of geometric mean, and range, instead of ~CV%, are presented (*n* = number of observations). Abbreviations: Geo mean, geometric mean; NC, not calculated.

BAY 43-9006 has a long half-life and accumulates 4- to 6-fold on multiple dosing, suggesting than once-daily dosing may be appropriate for this agent. However, previous findings show that bid dosing seems to overcome saturation of absorption thereby leading to higher exposure than once-daily dosing: in a phase I study using a continuous dosing schedule of 200 mg BAY 43-9006 daily, BAY 43-9006 $AUC_{0-\infty}$ values were, on average, 2-fold greater following bid dosing compared with once-daily dosing (11). Additionally, bid dosing would have greater C_{min} values than once-daily dosing. When combined with the results of three other phase I studies, the results of this evaluation show that the bid dosing schedule produced

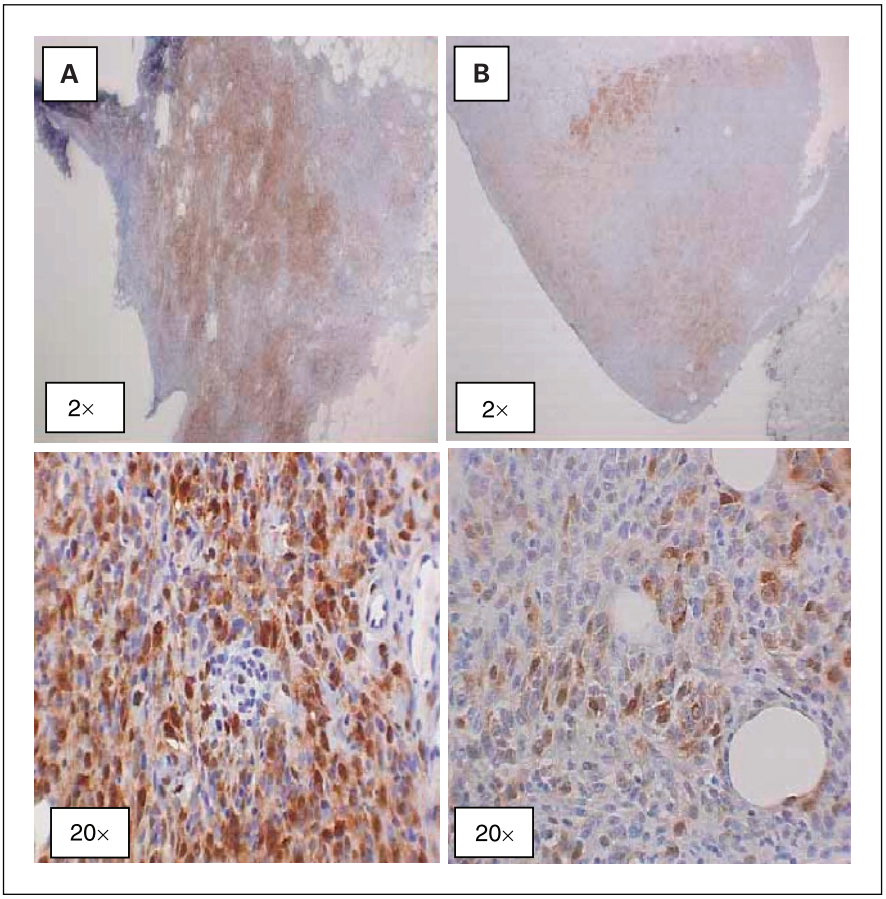

Fig. 2. pERK staining in biopsy specimens from a patient with melanoma at (*A*) day 1 of cycle 1 and (*B*) day 7 of cycle 2. 2Q = 26-50% nuclei staining; 4Q = 76-100% nuclei staining.

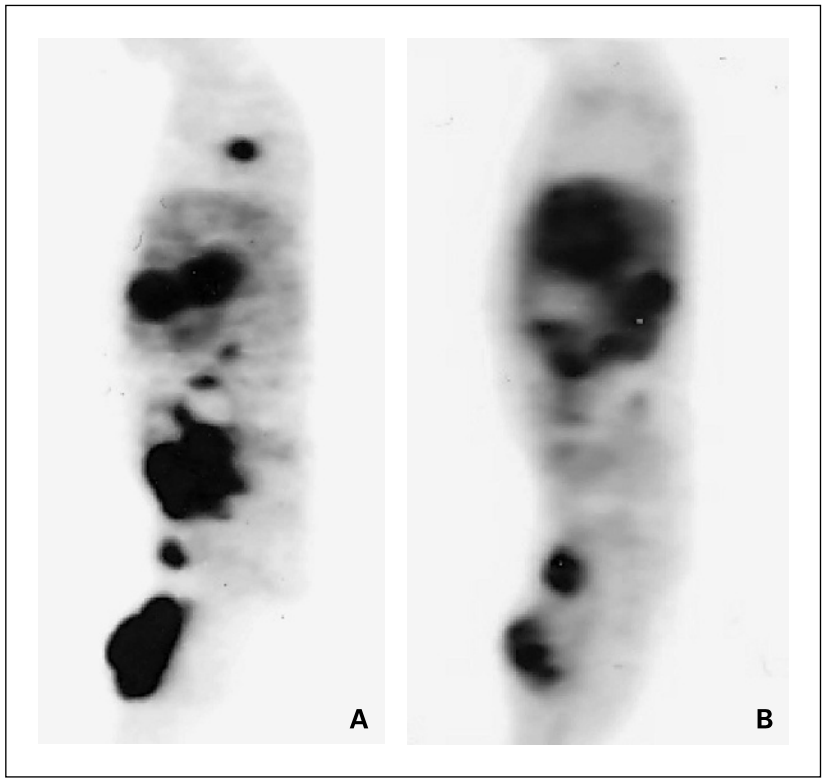

Fig. 3. Positron emission tomography scans of the melanoma tumor at baseline (*A*) and after cycle 18 (*B*) showing reduced uptake of [^{18}F]2-fluoro-2-deoxy-D-glucose, suggesting a reduction in tumor activity induced by BAY 43-9006 treatment.

consistently high and therapeutic BAY 43-9006 levels in individuals. Therefore, this is the schedule being used in ongoing phase II and III trials. Results from ongoing studies suggest that BAY 43-9006 may be safely given with drugs known to inhibit CYP3A-mediated metabolism, possibly because other metabolic pathways (i.e., glucuronidation) play a significant role in BAY 43-9006 metabolism.

BAY 43-9006 was well tolerated in most patients. Pruritus and rash/desquamation were the most common drug-related adverse events and were reported in at least two patients per group. Pruritus and rash occurred dose dependently and increased in severity and frequency at the 400 mg bid dose level and higher. Results from the three parallel phase I trials support the findings from this study that BAY 43-9006 is well tolerated in patients with advanced, refractory solid tumors, and that most adverse events are mild to moderate in severity (11).

The best response observed in this study was stable disease in five (26%) patients. This is similar to the best response seen in the three other phase I studies, from which stable disease rates of 37%, 55%, and 22% were reported (11). One patient with metastatic melanoma had a minor response, which lasted for ~9 weeks before progressing. Metastatic melanoma is known to have both a moderately high frequency of mutations in the *B-raf* gene (~60-70%; refs. 14, 15), and high expression of angiogenic markers, such as VEGFR (16), both of which are potential targets for BAY 43-9006. This patient showed a reduction in the frequency of pERK staining in tumor biopsies compared with baseline levels, in association with reduced tumor activity detected by positron emission tomography scans. This observation is consistent with targeted inhibition of the Raf/MEK/ERK pathway. A second patient with metastatic RCC remained on treatment with stable disease for ~2 years. Although specific mutations in *ras* and *B-raf* are less common in RCC, activation of the Raf/MEK/ERK pathway is implicated in the development of RCC (17), and high-level expression of angiogenic factors, such as VEGF, has been associated with disease progression (18). Therefore, RCC may be responsive to an agent such as BAY 43-9006, which targets Raf kinase and VEGFR.

In conclusion, the results of this study show the safety and pharmacokinetic profile of BAY 43-9006. The potential activity of BAY 43-9006 in patients with advanced, solid tumors is being evaluated further in ongoing phase II and III trials. The dual-targeted action of BAY 43-9006, against both tumor cell proliferation and angiogenesis, may be particularly promising in a wide range of tumor types with differing underlying pathophysiology.

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