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ORIGINAL REPORT

Phase II Placebo-Controlled Randomized Discontinuation Trial of Sorafenib in Patients With Metastatic Renal Cell Carcinoma

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ABSTRACT

Purpose
This phase II randomized discontinuation trial evaluated the effects of sorafenib (BAY 43-9006), an oral multikinase inhibitor targeting the tumor and vasculature, on tumor growth in patients with metastatic renal cell carcinoma.

Patients and Methods
Patients initially received oral sorafenib 400 mg twice daily during the initial run-in period. After 12 weeks, patients with changes in bidimensional tumor measurements that were less than 25% from baseline were randomly assigned to sorafenib or placebo for an additional 12 weeks; patients with ≥ 25% tumor shrinkage continued open-label sorafenib; patients with ≥ 25% tumor growth discontinued treatment. The primary end point was the percentage of randomly assigned patients remaining progression free at 24 weeks after the initiation of sorafenib.

Results
Of 202 patients treated during the run-in period, 73 patients had tumor shrinkage of ≥ 25%. Sixty-five patients with stable disease at 12 weeks were randomly assigned to sorafenib (n = 32) or placebo (n = 33). At 24 weeks, 50% of the sorafenib-treated patients were progression free versus 18% of the placebo-treated patients (P = .0077). Median progression-free survival (PFS) from randomization was significantly longer with sorafenib (24 weeks) than placebo (6 weeks; P = .0087). Median overall PFS was 29 weeks for the entire renal cell carcinoma population (n = 202). Sorafenib was readministered in 28 patients whose disease progressed on placebo; these patients continued on sorafenib until further progression, for a median of 24 weeks. Common adverse events were skin rash/desquamation, hand-foot skin reaction, and fatigue; 9% of patients discontinued therapy, and no patients died from toxicity.

Conclusion
Sorafenib has significant disease-stabilizing activity in metastatic renal cell carcinoma and is tolerable with chronic daily therapy.

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INTRODUCTION

Sorafenib (BAY 43-9006) is an oral kinase inhibitor targeting both tumor cells and the tumor vasculature. It was originally developed as an inhibitor of Raf-1, a member of the Raf/MEK/ERK signaling pathway.[1,2] Sorafenib was subsequently found to have activity against B-Raf, vascular endothelial growth factor receptor–2, platelet-derived growth factor receptor, Fms-like tyrosine kinase-3 (Flt-3), and stem-cell growth factor (c-KIT).[3] In phase I studies investigating various oral dosing schedules, sorafenib was generally well tolerated; the recommended dose for future trials was 400 mg bid continuously. Dose-limiting toxicities at continuous doses higher than 400 mg bid were diarrhea, fatigue, and skin toxicity.[4-7]

Preclinical studies in xenograft models (colon, breast, lung) showed that the primary effect of sorafenib was inhibition of tumor growth rather than tumor shrinkage.[3] These data suggested that, unlike cytotoxic agents, the primary clinical benefit of agents such as sorafenib may be disease stabilization. Therefore, classical oncology paradigms for phase II clinical evaluation (eg, single-arm noncontrolled studies using partial or complete response rate as the primary end point) would not adequately detect the activity of sorafenib.[8] As duration of

disease stabilization is affected by the natural history of the disease and the effect of any administered agent, drug effect is best measured through use of a placebo control, ideally with minimization of patient exposure to placebo.

The randomized discontinuation (or withdrawal) trial (RDT) design, first proposed in 1975, attempts to assess the clinical activity of a drug while minimizing the use of placebo.[9] Since then, this design has been used in many therapeutic areas.[10-15] This is an enrichment design, in which all patients receive study drug for an initial run-in period, followed by random assignment of potential responders to either the study drug or placebo.[9,14] This design creates a controlled trial without upfront randomization, and decreases the heterogeneity of the randomly assigned population, resulting in increased statistical power with smaller patient numbers. This design was first implemented in oncology in a study of carboxyaminoimidazole for the treatment of metastatic renal cell carcinoma (RCC).[16,17]

Our multicenter placebo-controlled RDT was performed to determine whether sorafenib inhibits tumor growth in patients with metastatic solid tumors who maintain stable disease after a 12-week run-in period. The original protocol focused on patients with metastatic colorectal carcinoma (CRC), based on the putative importance of Raf/MEK/ERK signaling in this tumor type.[18,19] However, the broad eligibility criteria of the protocol also enabled enrollment of patients with other malignancies. Early signs of antitumor activity in patients with RCC and low numbers of patients with CRC achieving the criteria for randomization after the 12-week run-in period led to a refocus of this study toward patients with RCC, as we have reported here.

PATIENTS AND METHODS

Patients

Patients with histologically or cytologically confirmed metastatic refractory cancer for which no approved effective therapy exists were eligible for this study. Originally, the study focused on patients with CRC, but allowed enrollment of patients with other solid tumor types. During the course of the study, evidence of tumor regression in many patients with RCC led to a protocol amendment, which extended recruitment of patients with RCC and terminated enrollment of patients with CRC.

Inclusion criteria included: patient age of at least 18 years; at least one measurable tumor; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; life expectancy of at least 12 weeks; and adequate bone marrow, liver, and renal function. Patients with other serious medical problems or CNS involvement were excluded. There was no limit on the extent of prior therapy, except for the exclusion of patients with previous exposure to a Ras pathway inhibitor.

Study Design

This RDT was conducted at five centers. Enrollment began on September 25, 2002. This report includes efficacy data up to December 31, 2004. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Sorafenib (Bayer Pharmaceuticals Corporation, West Haven, CT) was initially administered to all patients in a 12-week open-label run-in period using continuous oral dosing at 400 mg bid. Doses of sorafenib were delayed or reduced if clinically significant toxicities considered related to sorafenib occurred. After the 12-week run-in period, disease status was assessed based on change in bidimensional tumor measurements from baseline.[20] Patients with $\geq$ 25% tumor shrinkage continued to receive sorafenib until disease progression or toxicity, in order to avoid concerns about the random assignment of these patients. Patients with progressive disease ($\geq$ 25% tumor growth or other evidence of progression) discontinued treatment. Patients who had a change in tumor size of less than 25% were randomly assigned to either sorafenib (at current dose) or matching placebo in a double-blinded fashion, using centralized allocation via a telephone randomization system. Patients who progressed at any time after randomization (progression was defined as a change in bidimensional tumor measurement from randomization of $\geq$ 25% or clinically assessed progression) were unblinded. Patients whose disease progressed while on placebo were offered sorafenib, and patients on sorafenib discontinued treatment.

Assessment of Efficacy

The primary end point was the percentage of randomly assigned patients who remained progression free at 12 weeks following random assignment (24 weeks after study entry).

Secondary end points included progression-free survival (PFS) after random assignment (randomized subset only); overall PFS (from start of treatment); tumor response rate; and safety. Tumor response was assessed at 12 weeks, and once every 6 weeks thereafter, in accordance with modified WHO guidelines for partial response (PR), stable disease (SD), and progressive disease (PD). Objective responses were confirmed at least 4 weeks after the original documentation. In order to verify investigator observations in an unbiased manner, independent assessment of radiologic scans was performed retrospectively for 152 (75%) of 202 patients. Some scans were not available for independent assessment, as a radiology charter specifying parameters for independent review was developed after the last patient was accrued. These independent radiographic assessments were performed by RadPharm (Princeton, NJ).

Assessment of Safety

Safety was assessed for the entire treatment period (run-in plus randomization). All patients who received at least one dose of the study drug and who had post-treatment data available were assessable for safety. Safety assessments were performed every 3 weeks during the run-in and randomization phases, and once every 4 weeks thereafter. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0), and their relationship to the study drug was recorded.

Statistical Analysis

Simulations for computing power and sample size assumed that tumor growth was exponential and that the distribution of tumor growth rates was log-normal. The mean growth rate in these simulations led to 43% of patients with SD and 57% of patients with PD after 12 weeks, assuming no treatment effect. With 50 patients randomly assigned to each group, the study had a power of 81% to detect a drug effect that corresponded to a reduction in the progression rate from 90% to 70%, 12 weeks after randomization. This simulation did not consider the possibility of tumor shrinkage.[16]

For the primary efficacy end point, the two treatment groups (based on an intention to treat) were compared using a Cochran–Mantel-Haenszel test stratified by baseline ECOG score; 95% CIs were computed using binomial distribution. PFS after randomization was summarized by the Kaplan-Meier method, and was compared between treatment groups using a log-rank test. We estimated PFS attributable to sorafenib by piecing together information from the various treatment groups and treatment periods. All patients contributed to the PFS estimate for the first 12 weeks of therapy. We combined the PFS estimate for the first 12 weeks with a similar estimate for all remaining weeks after the first 12 weeks, the latter assuming the patient was alive and progression free at 12 weeks. We estimated PFS after 12 weeks as a weighted average of group-specific PFS for the two groups treated with sorafenib for more than 12 weeks: the 79 patients who entered the open-label part of the trial and the 33 patients randomly assigned to continue on sorafenib. When combining the group-specific PFS estimates, the weights corresponded to the fraction of patients continuing on open-label sorafenib at 12 weeks (79 of 144 patients) and the proportion of randomly assigned patients who were progression free at 12 weeks (65 of 144 patients).

RESULTS

This study design permitted enrollment of patients with a variety of tumor types; 502 patients were enrolled onto the study, 501 of whom received the

study drug. Early indications of activity in patients with RCC caused us to refocus our study on this patient population, resulting in RCC being the most predominant tumor type (202 patients [40%]).

The baseline demographics of these RCC patients are listed in Table 1. In the randomized phase, the distribution of men and women differed between the treatment groups. However, there were no significant differences between groups for this or any of the other measured baseline characteristics.

Response Assessment: Run-in Phase

Response was assessed at the end of the 12-week run-in based on investigator-assessed bidimensional tumor measurements. Response assessment was unavailable for nine patients (4%), all of whom had discontinued treatment before week 12. This response assessment was used to determine patients' subsequent course of therapy. A total of 73 patients (36%) achieved tumor shrinkage ≥ 25% compared with baseline, 69 patients (34%) had tumor measurements that remained

Table 1. Baseline Characteristics for All Treated Patients (n = 202)

Characteristic	All Patients (N = 202)		Patients by Random Assignment: Placebo Group (n = 33)		Patients by Random Assignment: Sorafenib Group (n = 32)	
	No.	%	No.	%	No.	%
Sex						
Male	149	74	21	64	26	81
Female	53	26	12	36	6	19
Age, years						
Median	58		60		58	
Range	23-83		23-74		32-76	
ECOG PS						
0	110	54	18	55	18	56
1	92	46	15	45	14	44
TNM stage						
I	21	10	3	9	2	6
II	49	24	6	18	11	34
III	49	24	8	24	9	28
IV	68	34	15	45	8	25
Missing	15	7	1	3	2	6
Histologic subtype						
Clear cell	152	75	25	76	27	84
Papillary	15	7	3	9	0	0
Other	11	5	2	6	1	3
Missing	24	12	3	9	4	13
MSKCC risk category*						
Low	69	34	14	42	13	41
Intermediate	121	60	15	45	18	56
High	6	3	3	9	0	0
Missing	6	3	1	3	1	3
No. of organ sites of disease						
1	32	16	4	12	8	25
2	77	38	15	45	7	22
≥ 3	93	46	14	42	17	53
Sites of disease†						
Lung	154	76	23	70	28	88
Lymph node	86	43	16	48	14	44
Kidney	70	35	15	45	12	38
Liver	52	26	10	30	5	16
Duration of disease						
No. of patients	198		33		31	
No. of years	2.6		2.8		3.3	
Range	0-21.9		0-11.7		0-21.2	
Prior therapy						
Systemic anticancer therapy	170	84	29	88	29	91
IL-2 or interferon	154	76	28	85	26	81
Non-diagnostic surgery	202	100	33	100	32	100
Radiotherapy	68	34	11	33	9	28
Nephrectomy	179	89	29	88	29	91

Abbreviatons: ECOG PS, Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan-Kettering Cancer Center (New York, NY); IL, interleukin.
*MSKCC risk category was assessed using four of the five original risk factors[29] as follows: low Karnofsky performance status (< 80%); low serum hemoglobin (< lower limit of normal); high corrected serum calcium (> 10 mg/dL); and absence of prior nephrectomy. High lactate dehydrogenase was omitted as a risk factor for the present study because lactate dehydrogenase measurements were not collected prospectively for all patients, and a more recent publication excluded high lactate dehydrogenase as an independent risk factor for survival.[30] Risk categories were defined as: high risk, ≥ 3 risk factors; intermediate risk, 1-2 risk factors; low risk, no risk factors.
†Target or non-target lesions for > 20% of all 202 patients.

within 25% of baseline levels, and 51 patients (25%) showed either tumor growth ≥ 25% or other evidence of progression at or before week 12 (Fig 1).

Eight patients (4%) had independently confirmed PRs by modified WHO criteria at 12 weeks, all of these patients continued on open-label treatment. Investigator-assessed PR rate by modified WHO criteria was 11%. Of the 15 patients treated with papillary cancer, investigator assessment of best response (using WHO criteria) showed two PRs at 12 weeks, with an additional three patients having tumor shrinkage of 25% to 49%.

Patient Disposition

The 12-week run-in was completed by 187 patients (93%). Of the 15 patients who discontinued treatment before the 12-week assessment, the majority (12 patients) did so because of adverse events; one patient withdrew consent, one patient was lost to follow-up, and one patient died (as a result of pneumonia and metastatic disease, unrelated to the study drug).

Of the 69 patients identified at 12 weeks with tumor growth or tumor shrinkage of less than 25% who were eligible for entry onto the randomized phase, two patients continued on open-label sorafenib (investigator protocol violation), and three patients withdrew (one patient each due to adverse events, to pursue other treatment options, and for clinical progression before random assignment). One patient who met the study criteria for PD at week 12 was randomly assigned instead of discontinuing treatment. Therefore, a total of 65 patients were randomly assigned to receive sorafenib (32 patients) or placebo (33 patients). Seventy-three patients with tumor shrinkage of at least 25% at the 12-week assessment entered into the open-label part of the trial, plus six additional patients who continued sorafenib, either at the discretion of the investigator or after being granted a waiver, despite having SD (n = 3) or PD (n = 2), or not receiving treatment for the entire run-in (n = 1). Therefore, a total of 79 patients continued open-label sorafenib. Forty-three patients, who completed the 12-week run-in, discontinued treatment at a later time point; 40 patients because of PD, and three patients who had SD (and withdrew from the study).

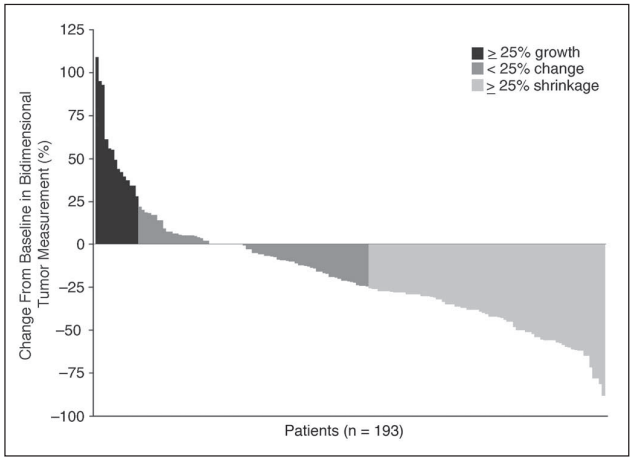

Fig 1. Changes from baseline in investigator-assessed, bidimensional radiographic measurements at 12 weeks for patients with renal cell carcinoma. These measurements were unconfirmed, and therefore do not represent confirmed responses according to modified WHO criteria. Mean change at 12 weeks was −18% (standard deviation, 33%).

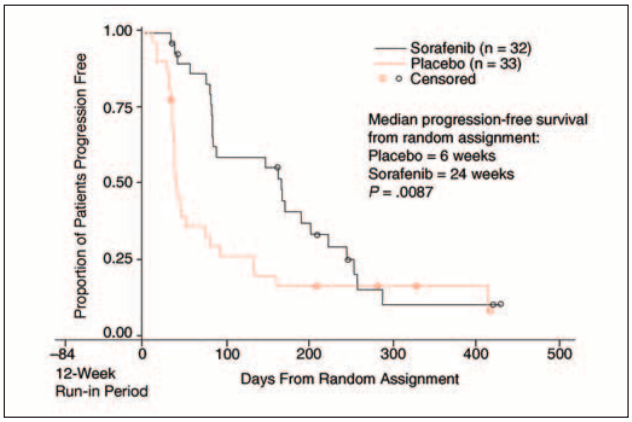

Fig 2. Kaplan-Meier plot of investigator-assessed progression-free survival from week 12 randomization for patients randomized to placebo (n = 33) or to sorafenib (n = 32).

Antitumor Activity

Randomized phase. At 12 weeks postrandomization (24 weeks from study entry), 50% of patients (16 of 32 patients) receiving sorafenib were progression free, compared with only 18%of patients (six of 33) receiving placebo ($P = .0077$). Median PFS from 12-week randomization was also statistically significantly longer in the sorafenib group (24 weeks) compared with the placebo group (6 weeks; $P = .0087$; Fig 2).

Sorafenib treatment was restarted in 28 patients whose disease progressed on placebo after a median time from randomization of 7 weeks. The median time from restarting sorafenib to the end of treatment in these patients was 24 weeks, suggesting restabilization of PD.

Entire treatment period. A secondary objective of this study was to estimate overall PFS for all treated patients. The 79 patients who continued on open-label sorafenib after 12 weeks had a median PFS from baseline of 40 weeks. In patients who achieved tumor shrinkage of at least 25% at 12 weeks (n = 73), PFS was not appreciably different in those patients who had tumor shrinkage of at least 25% to less than 50% (38 weeks; n = 45) with those patients who had tumor shrinkage of at least 50% (47 weeks; n = 28). This suggests that patients with minor tumor shrinkage may have the same

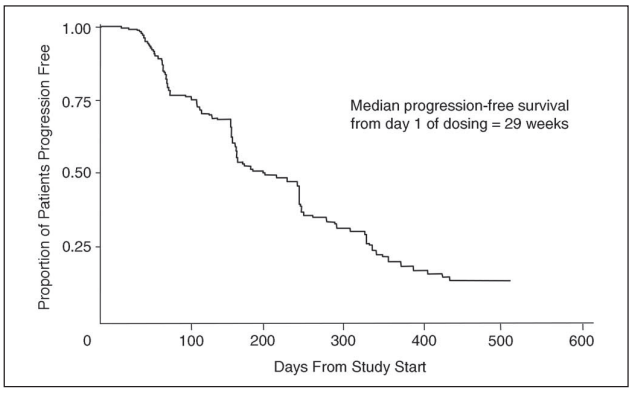

Fig 3. Kaplan-Meier plot of estimated overall progression-free survival for all treated patients (n = 202) from day 1 of study drug dosing (excluding placebo-treated patient data). See Patients and Methods for details on the calculations.

benefit as those with classic responses. For the entire population, median overall PFS was estimated (as described in Patients and Methods) to be 29 weeks (Fig 3).

Safety

The most common treatment-emergent adverse events were fatigue (73% of patients), rash/desquamation (66%), hand-foot skin reaction (62%), pain (other; 58%), and diarrhea (58%; Table 2). The majority of these events were grade 1 or 2 in severity, although nine patients discontinued drug because of toxicity. The most common grade 3/4 adverse event was hypertension, which was observed in 31% of patients. Antihypertensive therapy with a variety of agents was initiated in 46% of patients. No patients died from toxicity.

Table 2. Incidence of Adverse Events Reported for at Least 10% of Patients in the Total Safety Population (N = 202)

Adverse Events	Any Grade		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Any adverse event	202	100	108	53	25	12
Allergy/immunology	21	10	0	0	0	0
Blood/bone marrow	63	31	13	6	3	1
Hemoglobin	54	27	11	5	3	1
Cardiovascular (general)	114	56	69	34	2	1
Edema	30	15	0	0	0	0
Hypertension	86	43	62	31	0	0
Dermatology/skin	187	93	34	17	0	0
Alopecia	107	53	0	0	0	0
Dry skin	47	23	0	0	0	0
Flushing	32	16	0	0	0	0
Hand-foot skin reaction	125	62	27	13	0	0
Dermatology/skin, other	87	43	0	0	0	0
Rash/desquamation	134	66	5	2	0	0
Constitutional symptoms	181	90	17	8	1	< 1
Fever (in the absence of neutropenia)	24	12	0	0	0	0
Fatigue (lethargy, malaise, asthenia)	147	73	12	6	1	< 1
Weight loss	66	33	5	2	0	0
Constitutional symptoms, other	45	22	0	0	0	0
Gastrointestinal	192	95	26	13	2	1
Anorexia	95	47	6	3	0	0
Constipation	65	32	0	0	0	0
Diarrhea, patients without colostomy	117	58	8	4	0	0
Nausea	61	30	0	0	0	0
Gastrointestinal, other	58	29	6	3	1	< 1
Stomatitis/pharyngitis (oral/pharyngeal)	70	35	0	0	0	0
Vomiting	48	24	0	0	0	0
Renal/genitourinary	50	25	0	0	0	0
Creatinine	29	14	0	0	0	0
Hemorrhage	45	22	8	4	0	0
Hepatic	59	29	10	5	0	0
ALT	22	11	0	0	0	0
AST	23	11	0	0	0	0
Infection/febrile neutropenia	75	37	10	5	0	0
Infection without neutropenia	73	36	10	5	0	0
Musculoskeletal	29	14	0	0	0	0
Metabolic/laboratory	84	42	25	12	10	5
Hyperglycemia	34	17	5	2	1	< 1
Hyperuricemia	26	13	0	0	0	0
Hypophosphatemia	31	15	14	7	0	0
Neurology	97	48	8	4	4	2
Neuropathy, sensory	40	20	0	0	0	0
Pain	158	78	22	11	3	1
Abdominal pain or cramping	39	19	0	0	0	0
Headache	38	19	0	0	0	0
Arthralgia (joint pain)	25	12	0	0	0	0
Myalgia (muscle pain)	22	11	0	0	0	0
Pain, other	117	58	13	6	2	< 1
Pulmonary	127	63	17	8	4	2
Cough	57	28	0	0	0	0
Pulmonary, other	36	18	6	3	1	< 1
Dyspnea (shortness of breath)	77	38	15	7	3	1

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