Phase II Study to Investigate the Efficacy, Safety, and Pharmacokinetics of Sorafenib in Japanese Patients with Advanced Renal Cell Carcinoma

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Objective: Sorafenib (Nexavar®) is an oral multi-kinase inhibitor that targets tumor growth and angiogenesis. This phase II study investigated efficacy, safety, and pharmacokinetics of sorafenib in Japanese patients with advanced renal cell carcinoma (RCC).

Methods: Nonrandomized, open-label study in Japanese patients with metastatic renal cell carcinoma who had received nephrectomy and failed ≥1 cytokine-containing therapy. The primary endpoint was response rate. Patients received sorafenib 400 mg twice daily (b.i.d.) on a continuous dosing schedule.

Results: A total of 129 patients (median age 63 years) were valid for intention-to-treat analyses. Confirmed partial responses were observed in 16 (12.4%) patients, and investigators assessed that 19 (14.7%) of the patients achieved a partial response. Stable disease was reported in 93 (72.1%) patients, and 103 (80.5%) patients had tumor shrinkage. Median progression-free survival was 224 days and the 25th percentile of overall survival was estimated at 288 days. The most frequently occurring drug-related adverse events (any grade) were elevated lipase (56%), hand–foot skin reaction (55%), alopecia (39%), increased amylase (38%), rash/desquamation (37%), and diarrhea (34%). A total of 14 (10.7%) patients had serious sorafenib-related adverse events, including one adverse event of worst grade 5 (dyspnea occurred 35 days after the last dose of study medication). The Ctrough,steady state values in RCC patients (n = 63) receiving sorafenib 400 mg b.i.d. were similar to those obtained from a Japanese phase I study involving patients with mixed solid tumors.

Conclusion: Sorafenib showed encouraging efficacy and was well tolerated in Japanese patients with metastatic RCC.

Key words: sorafenib – Nexavar – BAY 43-9006 – clinical trial – Phase II – renal cell carcinoma – RCC

INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 3% of adult malignancies and 90–95% of neoplasms arising from the kidney (1). Clear-cell carcinoma is the most common histologic type of RCC, accounting for the majority (~70%) of cases (2). Approximately 30% of RCC patients present with advanced metastatic disease (3), which is often highly resistant to chemotherapy and is associated with a notoriously poor prognosis (1,4). Immunoreactive cytokines, interferon-alpha (IFN-α), and interleukin-2 (IL-2) have been the mainstay of treatment of RCC for more than 15 years (5). Studies have demonstrated objective responses of 10–20%, and 5-year survival rates of <20% with these immunotherapies in patients with advanced and metastatic RCC (1,4). Although a combination of IFN-α and IL-2 has recently demonstrated encouraging results for lung metastasis in Japanese patients with RCC (6), new therapies are needed to treat advanced RCC because of the relatively infrequent...
clinical activity and unsatisfactory safety profile of existing immunotherapies, and because there is a lack of treatment options for patients who have failed these therapies.

Clear-cell RCC is characterized by a loss of genetic material on chromosome 3p; 50% of tumors show somatic mutations in the von Hippel–Lindau (VHL) gene, and an additional 10–20% show inactivation of the VHL gene by epigenetic changes (e.g. hypermethylation) (2). Dysregulation of the VHL gene results in the overexpression and upregulation of proteins involved in tumor growth and neoangiogenesis, including those that activate the Raf/MEK/ERK signaling pathway, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) (7). Constitutive activation of Raf/MEK/ERK is associated with the development of RCC (8).

Sorafenib (Nexavar) is a novel, orally available, multi-kinase inhibitor that inhibits Raf-1 and receptor tyrosine kinases including VEGF receptors (VEGFR)-1/-2/-3, PDGF receptor-beta (PDGFR-β), c-Kit, Flt-3, and RET (9–11). Sorafenib has gained approval for use in advanced RCC in many countries, including the United States and Europe. Preliminary clinical activity, such as disease stabilization and evidence of tumor shrinkage, was observed with sorafenib throughout an extensive phase I clinical program involving patients with several tumor types, including RCC (12–15). In a phase II randomized discontinuation trial and the pivotal phase III Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGETs), sorafenib significantly prolonged progression-free survival (PFS) 2- to 4-fold vs placebo in patients with advanced RCC (16,17). Frequently reported adverse events of sorafenib are mostly grade 1/2 in severity and include dermatologic (rash and hand–foot skin reaction (HFSR)), gastrointestinal (diarrhea), and constitutional (fatigue) toxicities (16,17). The encouraging tolerability profile and clinical activity of sorafenib support its use in patients with advanced RCC.

We investigated the safety, pharmacokinetics, and efficacy of sorafenib in Japanese patients with metastatic RCC, who had received nephrectomy and failed at least one cytokine-containing regimen, in this pivotal phase II trial in Japan.

**Methods**

**Patients**

Japanese patients with histologically or cytologically confirmed metastatic RCC, who had received nephrectomy and failed at least one cytokine-containing regimen, were eligible for the study. Additional inclusion criteria included: male or female patients aged ≥18 years; presence of at least one measurable lesion (computerized tomography (CT) or magnetic resonance image (MRI)) as designated by Response Evaluation Criteria In Solid Tumors (RECIST); life expectancy of ≥12 weeks; Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1; intermediate or low risk as designated by the Motzer score (18) (<3); [high lactate dehydrogenase (>1.5 × upper limit of normal); low serum hemoglobin (<lower limit of normal); high corrected serum calcium (>10 mg/dl); adequate clinical laboratory test results; and written informed consent. Exclusion criteria included: previous malignancy; history or presence of metastatic brain or meningeal tumors; cardiac arrhythmias; ≥Grade 2 National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE) bacterial or fungal infection; history of human immunodeficiency virus or hepatitis B or C; seizure disorder; previous or concomitant therapies including chemotherapy, radiotherapy, or hormonal therapy within 30 days of study initiation; >3 regimens of previous RCC therapy (adjuvant included if it lasted >3 months); pregnancy or lactation; known or suspected allergy to study agent; and any condition, psychological or otherwise, that could interfere with the study or jeopardize the safety of patient.

**Study Design**

This was a nonrandomized, open-label, phase II study in Japanese patients with metastatic RCC who had received nephrectomy and failed at least one cytokine-containing therapy regimen. The primary endpoint was to determine the response rate, i.e. the proportion of patients with partial response (PR) plus complete response (CR), confirmed according to RECIST. Secondary endpoints were PFS, time to progression (TTP), overall survival, overall best response, overall response duration and time to objective response, and overall disease control rate (i.e. a best response of CR, PR, or stable disease according to RECIST that was maintained for ≥28 days after the first response was recorded). Patients received sorafenib 400 mg (two 200 mg tablets) orally, twice daily (b.i.d.; approximately 12 h apart) on a continuous dosing schedule. Treatment continued until disease progression, unacceptable toxicity, or death occurred. Dose modification (e.g. discontinuation, or 400 mg once daily (o.d.), or 400 mg o.d. every other day) was applied when the following criteria were met: nonhematologic toxicity (grade 3/4); elevated pancreatic enzymes (grade 4 elevation; pancreatitis; serious or life-threatening); skin toxicities (grade 3 HFSR); hematologic toxicity (grade 4 neutropenia); platelet count <25 000/μl; hypertension (grade 4 or uncontrollable).

**Efficacy Analysis**

Tumor measurements were performed according to RECIST at screening (within 28 days of study start), every 6 weeks for the first 24 weeks (or until disease progression), and every 8 weeks thereafter. For patients with unconfirmed PR or unconfirmed CR, a CT scan for confirmation was performed 4 weeks after the first recorded response. Lesions identified and measured at baseline were evaluated using the same technique, preferably by the same investigator. Tumor evaluation was reviewed by external independent specialists.
per RECIST guidelines. Disease progression was confirmed by radiography whenever possible; otherwise, it was determined by investigators’ clinical judgment. PFS was defined as the time from initiation of treatment to disease progression (radiological or clinical), or death. The overall disease control rate and the tumor response rate were also classified according to the Japanese Urological Association (JUA) evaluation criteria (e.g. the General Rule for Clinical and Pathological Studies on Renal Cell Carcinoma) (19).

SAFETY EVALUATION

Patients were monitored for adverse events at every visit, according to NCI-CTCAE version 3.0. All patients who had received at least one dose of sorafenib were evaluated for safety (brief physical examination and vital signs) and compliance with sorafenib every 3 weeks for the first 24 weeks, and every 4 weeks thereafter. All laboratory tests were performed in the principal medical center.

PHARMACOKINETICS

Blood samples for pharmacokinetic analyses were collected during week 6 before administration of study drug. C_{trough,steady-state} (ss) (drug concentration in plasma at the expected time to minimum concentration) data were categorized according to the following classification system: patient receives sorafenib 400 mg b.i.d. at week 6 without dose suspension or reduction, from study start to week 6 (classification A); patient receives sorafenib 400 mg b.i.d. at week 6 with dose suspension or reduction, from study start to week 6 (classification B); patient receives sorafenib 400 mg o.d. at week 6 with dose suspension or reduction, from study start to week 6 (classification C).

STATISTICAL ANALYSIS

Response rate was defined as the proportion of patients with confirmed CR and PR in the intent-to-treat (ITT) population. A two-stage procedure was applied, according to the Simon’s optimal design (20), using a one-sided $\alpha$ of 0.05 and a $\beta$ of 0.20 (the target response rate of interest was 7.5%, and the lower threshold response rate was 2.5%). Statistical analyses were performed at the first stage (54 patients: $\leq 1$ responder, evaluation of the efficacy with a response rate was closed; $\geq 2$ responders, the study proceeded to the final stage) and the final stage (108 patients: $\leq 5$ responders, the regimen was considered inactive; $\geq 6$ responders, the regimen was considered active). A point estimate and 95% confidence interval (CI) by the Motzer risk category of the response rate (18) were calculated. Kaplan–Meier and descriptive statistics were calculated for PFS, TTP, overall survival, duration of overall response, and time to objective response.

ETHICS

The design of this trial was agreed with the Pharmaceuticals and Medical Device Agency in July 2004. The protocol was approved by the appropriate Institutional Review Boards and/or Ethical Committee. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and the protocol complied with the requirements specified in Item 3 of Article 14 and Item 2 of Article 80 in the Pharmaceutical Affairs Law in Japan, and the Good Clinical Practice (GCP) issued on April 1, 1997.

RESULTS

PATIENT CHARACTERISTICS

From November 2004 to March 2006, a total of 173 patients were screened: 42 patients were judged ineligible for the study, and 131 patients were entered into the study and received at least one dose of sorafenib. Two patients were excluded from the ITT population for efficacy analyses due to violation of inclusion criteria. Of the remaining 129 patients valid for ITT analyses, 100 were male, and the median age was 63 years (range 30–83 years; Table 1). The most frequently occurring tumor subtypes were clear-cell carcinoma (86.8%), granular cell carcinoma (7.8%), and papillary RCC (3.9%) (Table 1). Median time from initial diagnosis to start of treatment was 2.6 years (range 0.3–17 years; Table 1). All patients had received prior nephrectomy and at least one cytokine therapy (IFN-α, 128; IL-2, 60), and 17 (13.2%) patients had received radiotherapy; of these, 72 (55.8%) patients had received IFN-α or IL-2 as palliative therapy (i.e. second-line or third-line therapy after disease progression with first-line treatment). A total of 56 (43.4%) patients required dose reductions or interruptions, of which 54 (96%) were due to adverse events. Median treatment duration was 28.1 weeks (range 0.6–56.1 weeks).

EFFICACY

Confirmed PRs, based on evaluation by an external committee according to RECIST, were observed in 16 (12.4%) patients and the response rate was 12.4% (95% CI: 7.3–19.4%; Table 2). Investigators assessed that 19 (14.7%) patients achieved a PR (e.g. response rate was 14.7%; 95% CI: 9.1–22.0%), and a total of 93 (72.1%) patients achieved stable disease (Table 2). The overall disease control rate (i.e. CR + PR or stable disease maintained for $\geq 28$ days) based on investigator assessment was 73.6% ($n = 95$; 95% CI 65.2–81.0%). During the study, a total of 103 (80.5%) patients had some degree of tumor shrinkage from baseline values (Fig. 1). Based on JUA evaluation, response rates were 26.4% (95% CI 19.0–34.8%) in eligible patients ($n = 129$) and 28.7% (95% CI: 19.9–39.0%) in patients who completed assessment according to these criteria ($n = 94$).
Based on investigator assessment, the median PFS was 224 days (95% CI 178–280 days; Figure 2). The 25th percentile of overall survival was estimated at 288 days. The median duration of response was 238 days, and the median time to response was 42 days (range 35–172 days) in the 19 patients with a best response of PR. PFS rate at 6 months after treatment was 59 and 88% in patients with stable disease and PR, respectively. A total of 28 deaths were reported among the 129 patients.

**SAFETY**

A total of 131 patients, who had received at least one dose of sorafenib, were valid for safety analysis. All patients (*n* = 131) experienced at least one treatment-emergent adverse event, of which 127 patients had an adverse event related to sorafenib (Table 3). The majority of adverse events were mild to moderate in severity (grades 1 and 2). The most frequently occurring drug-related adverse events, occurring in ≥10% of patients at any grade, were: elevated lipase (56%), HFSR (55%), rash/desquamation (37%), diarrhea (34%), alopecia (39%), increased amylase (38%), and hypertension (27%) (Table 3). The majority of hematological abnormalities, including those related to hemoglobin (69%), lymphopenia (61%), neutrophils (15%), and platelets (31%), were mostly of grade 1 or 2 severity (Table 4). Although a total of 81 (61.8%) patients had at least one grade 3–5 drug-related adverse event, grade 4/5 adverse events were relatively infrequent: 17 patients (13%) had at least one drug-related adverse event of worst grade 4 (lipase: eight cases), and one patient (0.8%) had one...
drug-related adverse event of worst grade 5 (dyspnea occurred 35 days after the last dose of study medication). Pulmonary events of grade 3–5 in severity were observed in three patients, but no interstitial pneumonitis was reported during clinical or radiological examinations. An analysis of cumulative event rates revealed that HFSR occurred relatively early in the course of sorafenib treatment: of the 72 patients with drug-related HFSR, 43 had new-onset HFSR during the first 3 weeks of treatment, 14 patients had this toxicity at week 6, nine patients at week 9, and fewer thereafter. A similar pattern was observed for rash/desquamation and pruritus. In contrast, the onset of alopecia was more gradual.

A total of 42 (32.1%) patients experienced at least one serious adverse event, of whom 14 (10.7%) patients had serious adverse events related to sorafenib. The most frequently occurring drug-related serious treatment-emergent adverse events were liver dysfunction, alanine transferase (ALT) elevation, and aspartate transferase (AST) elevation, each of which was reported in three patients (2.3%).

A total of 56 (42.7%) patients discontinued treatment due to disease progression, and 10 (7.6%) patients discontinued treatment due to adverse events. Eight deaths occurred within 30 days of the last study-drug administration.

PHARMACOKINETICS

A total of 72 patients were evaluable for $C_{\text{trough,ss}}$ values. $C_{\text{trough,ss}}$ values in patients with no dose modifications at week 6 (3.03 mg/l) were similar to those in patients who had at least one dose modification, but were still receiving 400 mg b.i.d. in week 6 (3.38 mg/l) (Table 5). $C_{\text{trough,ss}}$ decreased by approximately 50% (1.44 mg/l) in patients who had received at least one dose modification and were being treated with 400 mg o.d. in week 6, compared with those on the b.i.d. dosing schedule (Table 5). The $C_{\text{trough,ss}}$ value in RCC patients who had not received any dose modification by week 6 (3.03 mg/l) was similar to that obtained at steady state (on day 14; before the morning dose) from a study (no. 11497) involving Japanese patients with progressive mixed solid tumors (3.83 mg/l; range 1.22–14.77 mg/l) (21).

DISCUSSION

Encouraging anti-tumor activity was observed with sorafenib 400 mg b.i.d. as a second-line treatment in the present trial; 12.4% of patients achieved confirmed PRs, more than two-thirds of patients had stable disease, and 80.5% of patients had some degree of tumor shrinkage. These findings compare favorably with investigator-assessed efficacy of

<table>
<thead>
<tr>
<th>Table 3. Incidence of drug-related adverse events occurring in ≥10% of all patients who received at least one dose of sorafenib (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event category</td>
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<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Any event</td>
</tr>
<tr>
<td>Blood/bone marrow</td>
</tr>
<tr>
<td>Cardiac general</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Dermatology/skin</td>
</tr>
<tr>
<td>Alopecia</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Rash/desquamation</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Metabolic/laboratory</td>
</tr>
<tr>
<td>Amylase</td>
</tr>
<tr>
<td>Lipase</td>
</tr>
<tr>
<td>Metabolic/laboratory, other</td>
</tr>
<tr>
<td>Neurology</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Pulmonary/upper respiratory</td>
</tr>
<tr>
<td>Voice changes</td>
</tr>
</tbody>
</table>

Table 4. Incidences of hematological abnormalities of grade 3/4 reported in ≥2% of all patients by NCI CTCAE Version 3.0

<table>
<thead>
<tr>
<th>Event category</th>
<th>Any grade, n (%)</th>
<th>Grade 3, n (%)</th>
<th>Grade 4, n (%)</th>
<th>Grade 5, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>90 (68.7)</td>
<td>7 (5.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>80 (61.1)</td>
<td>11 (8.4)</td>
<td>4 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>20 (15.3)</td>
<td>4 (3.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Platelets</td>
<td>40 (30.5)</td>
<td>2 (1.5)</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 2. Kaplan–Meier of progression-free survival, based on investigator assessment (patients valid for intent-to-treat analysis).
The present study is consistent with that reported in other phase II/III trials involving advanced RCC patients, in which sorafenib was associated with more dermatologic toxicities (e.g. HFSR and rash/desquamation) and hypertension (16,17).

Pharmacokinetic analyses from a phase I study in patients with a range of advanced refractory solid tumors demonstrated that sorafenib was absorbed at a moderate rate after the first dose, with $C_{max}$ occurring at 2.5–12.5 h after administration (15). Subsequently, plasma concentrations decreased slowly (15). Substantial accumulation in plasma was observed following multiple b.i.d. administrations (15). Similar to the pharmacokinetic characteristics reported after single dosing, plasma exposure (area under curve (AUC) and $C_{max}$ Values) exhibited high interpatient variability after multiple doses of sorafenib b.i.d. (15). This large variability in pharmacokinetics observed in patients with mixed solid tumors is consistent with the pharmacokinetic properties reported in the present trial. Furthermore, the $C_{trough,ss}$ Values in RCC patients receiving sorafenib 400 mg b.i.d. observed in the present trial are similar to those obtained from a Japanese phase I study involving patients with a variety of solid tumor types. Taken together, these data suggest that there are no major differences in overall pharmacokinetics between advanced solid tumor patients and RCC patients.

In conclusion, this phase II study demonstrated that sorafenib is generally well tolerated in Japanese patients with metastatic RCC, with encouraging anti-tumor activity.

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**Table 5.** $C_{trough,ss}$ of sorafenib at Week 6 following multiple doses of 400 mg b.i.d.

<table>
<thead>
<tr>
<th>Classification</th>
<th>n</th>
<th>Geometric mean</th>
<th>Geometric CV%</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Patient with no dose modification (temporary discontinuation or reduction)</td>
<td>63</td>
<td>3.03</td>
<td>58.36</td>
<td>0.87–9.74</td>
</tr>
<tr>
<td><strong>B</strong> Patient with dose modification by week 6 and treated with 400 mg b.i.d. at week 6</td>
<td>5</td>
<td>3.38</td>
<td>38.99</td>
<td>2.52–5.99</td>
</tr>
<tr>
<td><strong>C</strong> Patient with dose modification by week 6 and treated with 400 mg o.d. at week 6</td>
<td>4</td>
<td>1.44</td>
<td>48.54</td>
<td>0.76–2.07</td>
</tr>
</tbody>
</table>

o.d., once daily; ss, steady state.

Table 5. $C_{trough,ss}$ of sorafenib at Week 6 following multiple doses of 400 mg b.i.d.
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Conflict of interest statement
One of the authors, Keiko Nakajima is an employee of Bayer Yakuhin Ltd.

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