

# Targeted therapy of renal cell carcinoma

*Treatment with two recently approved tyrosine kinase inhibitors is offering new hope to patients with metastatic disease*

## What's new, what's important

**Kidney cancer research is offering a beacon of real hope in medical oncology.** Work on this disease is clearly at the forefront of new targeted therapies and new classes of pharmaceuticals. Antiangiogenic agents and small-molecule inhibitors of Raf kinase, VEGF, PDGF, c-KIT, and m-TOR are being studied alone, in combination, and with traditional biologics such as interferon alpha. Because many patients have experienced prolonged stable disease and partial responses, these results may soon call into question the endpoints of clinical trials.

Kidney cancer research also clearly illustrates the convergence of novel therapy, advanced imaging, genomic analysis, and definitions of clinical benefit. Success in advanced disease is leading to a new round of large phase III randomized trials assessing the potential benefits of these drugs in the adjuvant setting after nephrectomy. Certainly, many challenges remain.

And yet, despite a statistically significant improvement in the 5-year overall survival rate to 65%, the number of new cases this year will reach nearly 39,000, and the number of lives lost will number some 13,000. **Starting on page 422, our Community Translations commentary by Dr. Nicholas Vogelzang, Director of the Nevada Cancer Institute, provides expert insight for community oncologists into newly approved therapies for kidney cancer** (bevacizumab, sorafenib, and sunitinib), as well as emerging treatments and some surprising toxicity data from the 2006 Annual Meeting of the American Society of Clinical Oncology. All of which makes this month's column essential to delivering quality care.

We welcome your feedback on your community experience in this area. Send comments to the Managing Editor at [r.gould@elsevier.com](mailto:r.gould@elsevier.com).

— Steven Tucker, MD  
Editor, Community Translations

**R**ecently, the US Food and Drug Administration approved two oral tyrosine kinase inhibitors, sunitinib (Sutent) and sorafenib (Nexavar), for use as single-agent therapy of metastatic renal cell carcinoma (RCC).<sup>1,2</sup> Both of these agents target multiple growth factors that play a significant role in the spread of RCC.

### Sunitinib

Regulatory approval of sunitinib was based on two phase II, single-arm, multicenter studies in which patients whose disease progressed despite prior cytokine-based therapy received 50 mg of sunitinib once daily. The agent was given in 4-week cycles, with 2 weeks off between cycles, until disease progression occurred or the patient withdrew from the study.

In all, 106 patients were enrolled in study 1 and 63 in study 2; 86%

and 94% of them, respectively, were white, and 65% were male. Median age was 57 years, and all patients had an ECOG (Eastern Cooperative Oncology Group) performance status of 0 or 1. Nephrectomy (required in study 1) had been performed in 97% of the patients. Some component of clear-cell histology (required in study 1) was present in 95% of patients. Overall, 52% of the patients had three or more metastatic sites, including the lungs (81% overall), liver (27% of patients in study 1 and 16% in study 2), and bone (25% in study 1 and 51% in study 2). Patients with known brain metastases or leptomeningeal disease were excluded. All patients had received one prior cytokine-based regimen.

Objective response rates and duration of response are shown in Table 1. The median duration of response in study 1 is premature, since disease pro-

gression had occurred in only 4 of 27 responding patients at the time of data cutoff. Although the data come from uncontrolled trials, the response rates and durations are quite remarkable for second-line therapy in metastatic RCC.

The most common grade 3 adverse events (among treatment-emergent adverse events of any grade occurring in  $\geq 10\%$  of patients) were fatigue (11%), hypertension (6%), diarrhea (5%), dyspnea (5%), mucositis/stomatitis (4%), and vomiting (4%). No grade 4 events were observed. In all, 15% of patients experienced a decrease in left ventricular ejection fraction below the lower limit of normal. Bleeding events occurred in 26% of patients, most commonly epistaxis; no tumor hemorrhage was observed. Overall, hypertension occurred in 28% of patients and caused

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**TABLE 1**

Objective response and response duration in patients with metastatic renal cell carcinoma receiving sunitinib

	Study 1 (n = 106)	Study 2 (n = 63)
Objective response rate, % (95% CI)	25.5 (17.5–34.9)	36.5 (24.7–49.6)
Median duration of response, wk (95% CI)	27.1 (24.4–???)*	54.0 (34.3–70.1)

CI = confidence interval.

All responses were partial responses. Response was assessed by a blinded core radiology laboratory in study 1 and by the investigators in study 2.

\* Data were not mature enough at interim analysis to determine the upper confidence limit.

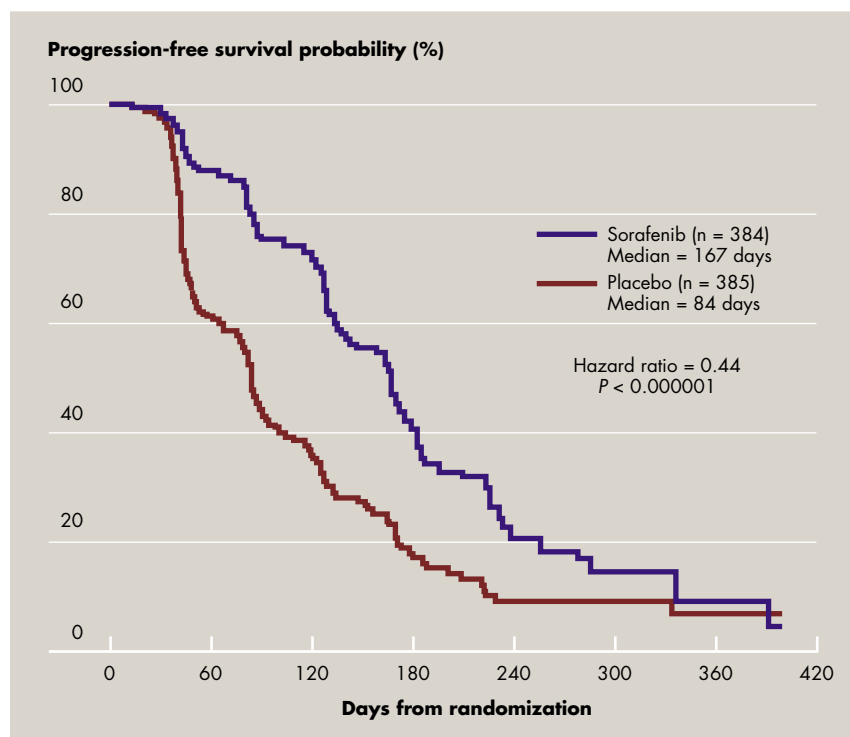
treatment delays in 4%.

## Sorafenib

Approval of sorafenib for advanced disease was based on a phase III trial and a phase II randomized discontinuation trial. In the international phase III trial, patients who had had one prior systemic treatment received oral sorafenib 400 mg twice daily (n = 384) or placebo (n = 385). Most patients were male (70%–75%), white (72%–73%), and under 65 years of age (67%–73%) and had an ECOG performance status of 0 or 1 (98%–99%) and prior interleukin-2 (aldesleukin [Proleukin]) or interferon

therapy (81%–83%); patients were approximately evenly divided in intermediate- and low-risk categories.

Progression-free survival, the primary endpoint, was significantly improved in patients receiving sorafenib (Figure 1), from a median of 84 to 167 days ( $P < 0.000001$ ). This improvement occurred in the context of partial response rates of 2% versus 0% in the sorafenib versus placebo groups. On interim analysis, sorafenib treatment was associated with a hazard ratio for overall survival of 0.72, which was not statistically significant; additional analyses are planned as data mature in the study population.



**FIGURE 1** Kaplan-Meier analysis of progression-free survival in patients with advanced renal cell carcinoma receiving sorafenib or placebo in a phase III trial.

In the phase II trial, patients with metastatic tumors, including RCC, received sorafenib for 12 weeks and then underwent radiologic reassessment. Patients with < 25% change in bidimensional tumor measurement were randomized to treatment with sorafenib or placebo for another 12 weeks, with those progressing on placebo being permitted to cross over to sorafenib. Patients with tumor shrinkage  $\geq 25\%$  continued on sorafenib, whereas those with tumor growth  $\geq 25\%$  were discontinued from the study. Of 202 patients with advanced RCC, 79 continued on open-label sorafenib and 65 were randomized to treatment with sorafenib or placebo after 12 weeks. At week 24, the progression-free rate was 50% in the 32 patients receiving sorafenib versus 18% in 33 receiving placebo ( $P = 0.0077$ ). Progression-free survival was 163 days in the sorafenib group, compared with 41 days in the placebo group (hazard ratio, 0.29;  $P = 0.0001$ ).

Hand-foot skin reaction and rash were the most common adverse events attributed to sorafenib treatment. In the phase III trial, hypertension occurred in 16.9% of sorafenib-treated patients versus 1.8% of patients given placebo, bleeding events occurred in 15.3% versus 8.2%, and cardiac ischemia/infarction events occurred in 2.9% versus 0.4%, respectively. Among a total of 451 patients with RCC receiving sorafenib, the most frequent severe toxicities (from among adverse events occurring in 10% or more of patients in the phase III trial) were hand-foot skin reaction (6% grade 3, 0% grade 4), fatigue (5% grade 3, < 1% grade 4), hypertension (3% grade 3, < 1% grade 4), and dyspnea (3% grade 3, < 1% grade 4).

## References

1. Nexavar [package insert]. West Haven, Conn: Bayer Pharmaceuticals Corp; 2005.
2. Sutent [package insert]. New York, NY: Pfizer Inc; 2006.
3. Escudier B, Szczylik C, Eisen T, et al. Randomized phase III trial of the multi-kinase inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC). *Eur J Cancer* 2005;3(suppl):226.

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