

## ORIGINAL ARTICLE

# Temsirolimus, Interferon Alfa, or Both for Advanced Renal-Cell Carcinoma

Gary Hudes, M.D., Michael Carducci, M.D., Piotr Tomczak, M.D.,  
Janice Dutcher, M.D., Robert Figlin, M.D., Anil Kapoor, M.D.,  
Elzbieta Staroslawska, M.D., Jeffrey Sosman, M.D., David McDermott, M.D.,  
István Bodrogi, M.D., Zoran Kovacevic, M.D., Vladimir Lesovoy, M.D.,  
Ingo G.H. Schmidt-Wolf, M.D., Olga Barbarash, M.D., Erhan Gokmen, M.D.,  
Timothy O'Toole, M.S., Stephanie Lustgarten, M.S.,  
Laurence Moore, M.D., Ph.D., and Robert J. Motzer, M.D.,  
for the Global ARCC Trial\*

## ABSTRACT

**BACKGROUND**

Interferon alfa is widely used for metastatic renal-cell carcinoma but has limited efficacy and tolerability. Temsirolimus, a specific inhibitor of the mammalian target of rapamycin kinase, may benefit patients with this disease.

**METHODS**

In this multicenter, phase 3 trial, we randomly assigned 626 patients with previously untreated, poor-prognosis metastatic renal-cell carcinoma to receive 25 mg of intravenous temsirolimus weekly, 3 million U of interferon alfa (with an increase to 18 million U) subcutaneously three times weekly, or combination therapy with 15 mg of temsirolimus weekly plus 6 million U of interferon alfa three times weekly. The primary end point was overall survival in comparisons of the temsirolimus group and the combination-therapy group with the interferon group.

**RESULTS**

Patients who received temsirolimus alone had longer overall survival (hazard ratio for death, 0.73; 95% confidence interval [CI], 0.58 to 0.92;  $P=0.008$ ) and progression-free survival ( $P<0.001$ ) than did patients who received interferon alone. Overall survival in the combination-therapy group did not differ significantly from that in the interferon group (hazard ratio, 0.96; 95% CI, 0.76 to 1.20;  $P=0.70$ ). Median overall survival times in the interferon group, the temsirolimus group, and the combination-therapy group were 7.3, 10.9, and 8.4 months, respectively. Rash, peripheral edema, hyperglycemia, and hyperlipidemia were more common in the temsirolimus group, whereas asthenia was more common in the interferon group. There were fewer patients with serious adverse events in the temsirolimus group than in the interferon group ( $P=0.02$ ).

**CONCLUSIONS**

As compared with interferon alfa, temsirolimus improved overall survival among patients with metastatic renal-cell carcinoma and a poor prognosis. The addition of temsirolimus to interferon did not improve survival. (ClinicalTrials.gov number, NCT00065468.)

From the Fox Chase Cancer Center, Philadelphia (G.H.); Sidney Kimmel Comprehensive Cancer Center, Baltimore (M.C.); Klinika Onkologii, Oddzial Chemioterapii, Poznań, Poland (P.T.); Our Lady of Mercy Medical Center, Bronx, NY (J.D.); University of California, Los Angeles, Los Angeles (R.F.); McMaster University, Hamilton, ON, Canada (A.K.); Lublin Oncological Center, Lublin, Poland (E.S.); Vanderbilt University Medical Center, Nashville (J.S.); Beth Israel Deaconess Medical Center, Boston (D.M.); National Institute of Oncology, Budapest, Hungary (I.B.); Military Medical Academy, Belgrade, Serbia (Z.K.); Regional Clinical Center of Urology and Nephrology, Kharkov, Ukraine (V.L.); University of Bonn, Bonn, Germany (I.G.H.S.-W.); Kemerovo State Medical Academy, Regional Clinical Hospital, Kemerovo, Russia (O.B.); Ege University Medical Faculty, Izmir, Turkey (E.G.); Wyeth Research, Cambridge, MA (T.O., S.L., L.M.); and Memorial Sloan-Kettering Cancer Center, New York (R.J.M.). Address reprint requests to Dr. Hudes at the Department of Medical Oncology, Rm. 307, Fox Chase Cancer Center, 333 Cottman Ave., Philadelphia, PA 19111, or at gary.hudes@fccc.edu.

\*Members of the Global Advanced Renal-Cell Carcinoma (ARCC) Trial are listed in the Appendix.

N Engl J Med 2007;356:2271-81.  
Copyright © 2007 Massachusetts Medical Society.

**R**ENAL-CELL CARCINOMA ACCOUNTS FOR 2.6% of all cancers in the United States, and nearly 39,000 new cases of this disease and 13,000 associated deaths were expected in 2006.<sup>1</sup> Surgical resection is the mainstay of treatment for tumors that are confined to the kidney. Distant metastases develop in about one third of patients, and most of these cases cannot be cured. Interleukin-2 and interferon alfa, alone or in combination, are the main treatments for metastatic renal-cell carcinoma. Treatment with these agents results in a median survival of 12.0 to 17.5 months.<sup>2-6</sup> These cytokines, however, have limited efficacy and substantial toxicity, and they rarely benefit patients with an extensive tumor burden and adverse prognostic factors. Such patients have a median survival of only 4 to 8 months.<sup>7-9</sup>

Temsirolimus (CCI-779) is an inhibitor of mammalian target of rapamycin (mTOR) kinase, a component of intracellular signaling pathways involved in the growth and proliferation of cells<sup>10,11</sup> and the response of such cells to hypoxic stress.<sup>12</sup> Temsirolimus binds to an abundant intracellular protein, FKBP-12, and in this way forms a complex that inhibits mTOR signaling.<sup>13,14</sup> The disruption of mTOR signaling suppresses the production of proteins that regulate progression through the cell cycle<sup>15,16</sup> and angiogenesis.<sup>17,18</sup> The inhibition of angiogenesis by temsirolimus is clinically relevant because unregulated angiogenesis is prominent in renal-cell carcinoma.<sup>19</sup>

Control of advanced renal-cell carcinoma was observed over a broad dose range in phase 1 trials of temsirolimus.<sup>20,21</sup> A phase 2 study of temsirolimus in cytokine-refractory metastatic renal-cell carcinoma showed evidence of improved survival,<sup>22</sup> and a study of temsirolimus plus interferon alfa identified tolerable doses and clinical indications of antitumor activity.<sup>23</sup> Encouraged by these results, we conducted a phase 3 trial in which we compared temsirolimus alone or temsirolimus plus interferon alfa with interferon alfa alone in metastatic renal-cell carcinoma.

## METHODS

### PATIENTS

Eligibility criteria included histologically confirmed advanced renal-cell carcinoma (stage IV or recurrent disease) and a Karnofsky performance score of 60 or more (on a scale of 0 to 100, with higher scores indicating better performance), with no previous systemic therapy. Additional eligibility cri-

teria were a tumor that was measurable according to the Response Evaluation Criteria in Solid Tumors (RECIST),<sup>24</sup> and adequate bone marrow, renal, and hepatic functions, which were defined as a neutrophil count of at least 1500 cells per cubic millimeter, a platelet count of at least 100,000 cells per cubic millimeter, and a hemoglobin count of at least 8 g per deciliter; a serum creatinine level of no more than 1.5 times the upper limit of the normal range; an aspartate aminotransferase level of no more than 3 times the upper limit of the normal range ( $\leq 5$  times if liver metastases were present); and a total bilirubin level of no more than 1.5 times the upper limit of the normal range. A fasting level of total cholesterol of no more than 350 mg per deciliter (9.1 mmol per liter) and a triglyceride level of no more than 400 mg per deciliter (4.5 mmol per liter) were required. Patients with a history of brain metastases were eligible if their condition was neurologically stable and they did not require corticosteroids after surgical resection or radiotherapy.

At least three of the following six predictors of short survival were required: a serum lactate dehydrogenase level of more than 1.5 times the upper limit of the normal range, a hemoglobin level below the lower limit of the normal range; a corrected serum calcium level of more than 10 mg per deciliter (2.5 mmol per liter), a time from initial diagnosis of renal-cell carcinoma to randomization of less than 1 year, a Karnofsky performance score of 60 or 70, or metastases in multiple organs.

Wyeth Research designed the trial and developed the study protocol in collaboration with the principal academic investigators. Data were collected and analyzed by Wyeth Research and the academic investigators. Radiologic assessments were performed by the study investigators and Bio-Imaging Technologies. The academic investigators were responsible for the decision to publish the data. All the authors had access to the primary data and vouch for the integrity and completeness of the data reported in this article. Dr. Hudes drafted the manuscript and revised it on the basis of suggestions from the coauthors. The sponsor played no role in writing or revising the manuscript.

The institutional review board at each participating center approved the study protocol, and the study was conducted in accordance with international standards of good clinical practice. All patients provided written informed consent.

**TREATMENT**

Patients were stratified according to the geographic location of the center (United States; Western Europe, Australia, and Canada; or Asia-Pacific, Eastern Europe, Africa, and South America) and whether they had undergone nephrectomy. Patients were randomly assigned in equal proportions, with the use of permuted blocks of three, to one of three treatment groups.

The interferon group received interferon alfa-2a (Roferon-A, Roche) at a starting dose of 3 million U given subcutaneously three times per week for the first week. The dose was raised to 9 million U three times per week for the second week and to 18 million U three times per week for week 3, if this dose was tolerated. Patients who were unable to tolerate 9 million U or 18 million U received the highest tolerable dose, which could be 3 million U, 4.5 million U, or 6 million U.

The temsirolimus group received 25 mg of temsirolimus (Wyeth Research) in a weekly 30-minute intravenous infusion. Premedication with 25 to 50 mg of intravenous diphenhydramine or a similar H<sub>1</sub> blocker was given approximately 30 minutes before each weekly temsirolimus infusion as prophylaxis against an allergic reaction. The combination-therapy group received 15 mg of temsirolimus in a 30-minute infusion weekly plus interferon at a starting dose of 3 million U three times per week for week 1 and 6 million U subcutaneously three times per week thereafter.

Treatment was continued as long as there was no disease progression, symptomatic deterioration, or intolerable adverse events. It was withheld for grade 3 or 4 adverse events (defined according to the National Cancer Institute Common Toxicity Criteria, version 3.0) and restarted at a reduced dose after recovery to grade 2 or lower. For the combination-therapy group, one or both agents were withheld, depending on the adverse event. For grade 2 adverse events that were poorly tolerated, dose reduction without treatment interruption was permitted at the discretion of the treating physician. Dose reduction was not required for adverse events that could be managed with supportive therapy.

**EVALUATION**

At baseline, a complete blood count was performed, along with assessments of levels of serum cholesterol and triglycerides and renal and hepatic function. Adverse events, serum chemical analyses, and blood counts were monitored weekly or biweekly.

Required imaging studies before treatment included computed tomographic (CT) scans of the chest, abdomen, and pelvis; a radionuclide bone scan; and a magnetic resonance imaging or CT scan of the brain. Scanning was repeated at 8-week intervals to evaluate tumor size. Response to treatment was assessed with the use of RECIST.

**STATISTICAL ANALYSIS**

The primary end point was overall survival, calculated on an intention-to-treat basis. We targeted a 40% improvement in median overall survival, from 4.9 months for interferon alone to 6.9 months for either of the temsirolimus-containing regimens. The planned sample size of 200 patients per group was based on a power of 80% to detect a 40% improvement for each comparison with the use of a two-sided stratified log-rank test at an overall 2.5% level of significance, with two planned interim analyses after approximately 164 and 430 deaths had occurred, and a final analysis, if necessary, after a total of 504 deaths had occurred.

Secondary efficacy end points were progression-free survival as determined by the site investigators' assessment and a blinded assessment of imaging studies (performed by Bio-Imaging Technologies), the objective response rate, and the clinical benefit rate, defined as the proportion of patients with stable disease for at least 24 weeks or an objective response. All patients who received any treatment were included in the analysis of safety. The characteristics of the patients in each group were compared with the use of the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. The proportion of patients with adverse events in each group was analyzed with the use of Fisher's exact test.

We explored the potential effect of the baseline characteristics of patients on progression-free and overall survival. The prespecified factors included age, sex, geographic region, nephrectomy status, tumor histologic type, time from metastasis to randomization, Karnofsky performance score, and levels of hemoglobin, serum lactate dehydrogenase, and corrected serum calcium. These analyses were performed by testing for a nonzero interaction between the treatment group and the baseline variable in a stratified Cox proportional-hazards model that included the treatment group, baseline factors, and their interaction as explanatory variables. We conducted separate analyses for the comparison of the temsirolimus group with the

| Characteristic   | Interferon<br>(N=207) | Temsirolimus<br>(N=209) | Interferon plus<br>Temsirolimus<br>(N=210) | Total<br>(N=626) |
|--|-----------------------|-------------------------|--|------------------|
| <b>Age</b>   |                       |                         |  |                  |
| Median — yr  | 60                    | 58                      | 59   | 59               |
| Range — yr   | 23–86                 | 32–81                   | 32–82                                      | 23–86            |
| <65 yr — no. (%)   | 142 (69)              | 145 (69)                | 153 (73)                                   | 440 (70)         |
| ≥65 yr — no. (%)   | 65 (31)               | 64 (31)                 | 57 (27)                                    | 186 (30)         |
| <b>Sex — no. (%)</b>   |                       |                         |  |                  |
| Male   | 148 (71)              | 139 (66)                | 145 (69)                                   | 432 (69)         |
| Female   | 59 (28)               | 70 (33)                 | 65 (31)                                    | 194 (31)         |
| <b>Karnofsky performance score — no. (%)</b>                 |                       |                         |  |                  |
| >70  | 34 (16)               | 41 (20)                 | 33 (16)                                    | 108 (17)         |
| ≤70  | 171 (83)              | 168 (80)                | 177 (84)                                   | 516 (82)         |
| <b>Previous nephrectomy — no. (%)</b>                        |                       |                         |  |                  |
|  | 139 (67)              | 139 (66)                | 141 (67)                                   | 419 (67)         |
| <b>Tumor histologic type — no. (%)</b>                       |                       |                         |  |                  |
| Clear-cell   | 170 (82)              | 169 (81)                | 163 (78)                                   | 502 (80)         |
| Other  | 37 (18)               | 40 (19)                 | 47 (22)                                    | 124 (20)         |
| <b>Protocol-defined poor prognostic features — no. (%)</b>   |                       |                         |  |                  |
| Lactate dehydrogenase level >1.5 times upper limit of normal | 48 (23)               | 36 (17)                 | 33 (16)                                    | 117 (19)         |
| Hemoglobin level <lower limit of normal                      | 168 (81)              | 172 (82)                | 178 (85)                                   | 518 (83)         |
| Corrected serum calcium level >10 mg/dl (2.5 mmol/liter)     | 72 (35)               | 54 (26)                 | 58 (28)                                    | 184 (29)         |
| Time from initial diagnosis to randomization <1 yr           | 164 (79)              | 174 (83)                | 179 (85)                                   | 517 (83)         |
| Karnofsky performance score ≤70†                             | 171 (83)              | 168 (80)                | 177 (84)                                   | 516 (82)         |
| ≥2 sites of organ metastasis                                 | 165 (80)              | 166 (79)                | 168 (80)                                   | 499 (80)         |
| <b>No. of poor prognostic features — no. (%)</b>             |                       |                         |  |                  |
| ≥3 of 6  | 196 (95)              | 195 (93)                | 198 (94)                                   | 589 (94)         |
| <3 of 6  | 11 (5)                | 14 (7)                  | 12 (6)                                     | 37 (6)           |
| <b>MSKCC risk classification — no. (%)‡</b>                  |                       |                         |  |                  |
| Poor risk (≥3 of 5 factors)                                  | 157 (76)              | 145 (69)                | 160 (76)                                   | 462 (74)         |
| Intermediate risk (1 or 2 of 5 factors)                      | 50 (24)               | 64 (31)                 | 50 (24)                                    | 164 (26)         |

\* Percentages may not total 100 because of rounding.

† A Karnofsky performance score of 70 (scores range from 0 to 100, with higher scores indicating better performance) signifies that the patient is unable to work but is able to perform activities of daily living.

‡ The Memorial Sloan-Kettering Cancer Center (MSKCC) model includes the first five poor-prognostic features listed in the table.

interferon group and for the comparison of the combination-therapy group with the interferon group.

Statistical analysis was performed by the study's sponsor, Wyeth Research. An independent data and safety monitoring committee reviewed the

study at 6-month intervals and at the predefined event milestones for the interim analyses. We report here on the results of the second interim analysis, conducted after 446 patients had died. On the basis of these data, the committee determined that the O'Brien–Fleming condition<sup>25</sup> for

early acceptance of the alternative hypothesis was reached, and the data were released to the sponsor. The significance level for stopping the study at the second interim analysis was  $P < 0.0135$ . All reported  $P$  values are two-sided and have not been adjusted for multiple testing.

RESULTS

From July 2003 to April 2005, a total of 626 patients were enrolled in the study. We randomly assigned 207 of these patients to receive interferon, 209 to receive temsirolimus, and 210 to receive a combination of interferon and temsirolimus. A total of 45 patients were ineligible (15 in the interferon group, 17 in the temsirolimus group, and 13 in the combination-therapy group), and 10 patients did not receive any treatment (7 in the interferon group, 1 in the temsirolimus group, and 2 in the combination-therapy group).

CHARACTERISTICS OF THE PATIENTS

Table 1 shows that the three treatment groups were well balanced on the basis of age, sex, and performance-status score. Approximately 80% of patients in each group had a Karnofsky performance score of 60 or 70. Clear-cell carcinoma was the histology of the tumor in approximately 80% of patients. Two thirds of the patients had undergone nephrectomy, and approximately 80% had received a diagnosis of metastatic disease within 12 months before enrollment. Three or more poor prognostic factors were present in 94% of the patients. A total of 19 patients were lost to follow-up (10 in the interferon group, 4 in the temsirolimus group, and 5 in the combination-therapy group).

EFFICACY

As compared with interferon alone, treatment with temsirolimus alone was associated with a hazard ratio for death of 0.73 (95% confidence interval [CI], 0.58 to 0.92;  $P = 0.008$ ). As compared with interferon, the combination of interferon plus temsirolimus resulted in a hazard ratio for death of 0.96 (95% CI, 0.76 to 1.20;  $P = 0.70$ ). Figure 1A shows the overall survival times in the three groups. Median survival was 7.3 months in the interferon group, 10.9 months in the temsirolimus group, and 8.4 months in the combination-therapy group (Table 2). As determined by the site investigators, the median progression-free survival times in the

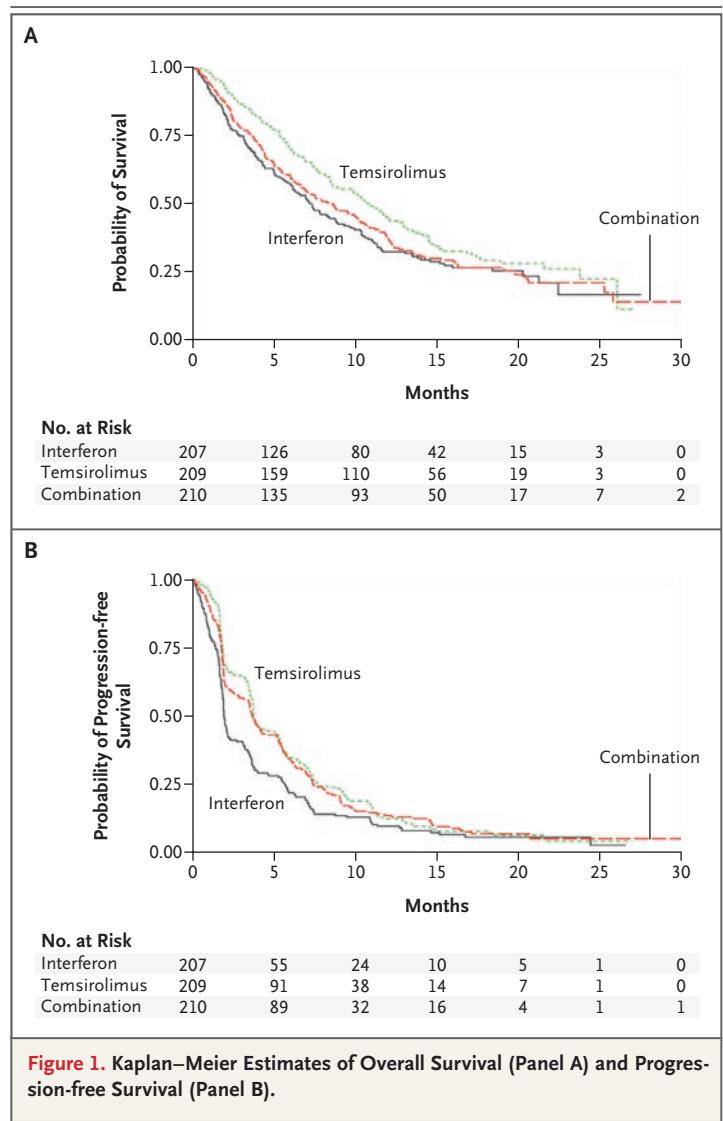


Figure 1. Kaplan–Meier Estimates of Overall Survival (Panel A) and Progression-free Survival (Panel B).

interferon, temsirolimus, and combination-therapy groups were 1.9, 3.8, and 3.7 months, respectively (Fig. 1B). According to the independent radiologic assessments, the median progression-free survival times for the interferon, temsirolimus, and combination-therapy groups were 3.1, 5.5, and 4.7 months, respectively. The shorter estimate of progression-free survival by the site investigators reflected the inclusion of patients with symptomatic deterioration that had begun before scheduled radiologic measurements of the tumor.

The objective response rates of 4.8%, 8.6%, and 8.1% among patients receiving interferon, temsirolimus, and combination therapy, respectively, did

**Table 2. Summary of Efficacy Measures.**

| End Point  | Interferon<br>(N = 207) | Temsirolimus<br>(N = 209) | Interferon plus<br>Temsirolimus<br>(N = 210) |
|--|-------------------------|---------------------------|--|
| Median overall survival — mo (95% CI)  | 7.3 (6.1–8.8)           | 10.9 (8.6–12.7)           | 8.4 (6.6–10.3)                               |
| Median progression-free survival — mo (95% CI)                                   |                         |                           |  |
| Site investigators' assessment   | 1.9 (1.9–2.2)           | 3.8 (3.6–5.2)             | 3.7 (2.9–4.4)                                |
| Independent assessment*  | 3.1 (2.2–3.8)           | 5.5 (3.9–7.0)             | 4.7 (3.9–5.8)                                |
| Median time to treatment failure — mo (95% CI)†                                  | 1.9 (1.7–1.9)           | 3.8 (3.5–3.9)             | 2.5 (1.9–3.6)                                |
| Objective response rate — % (95% CI)*  | 4.8 (1.9–7.8)           | 8.6 (4.8–12.4)            | 8.1 (4.4–11.8)                               |
| Clinical benefit (objective response or stable disease for ≥24 wk) — % (95% CI)* | 15.5 (10.5–20.4)        | 32.1 (25.7–38.4)          | 28.1 (22.0–34.2)                             |

\* This category includes only patients who underwent tumor assessment after the baseline assessment: 153 patients in the interferon group (74%), 192 patients in the temsirolimus group (92%), and 168 patients in the combination-therapy group (80%).

† The time to treatment failure was determined by the site investigators.

not differ significantly (Table 2). By contrast, the proportion of patients with stable disease for at least 6 months or an objective response was greater in the temsirolimus group (32.1%) and the combination-therapy group (28.1%) than in the interferon group (15.5%) ( $P < 0.001$  and  $P = 0.002$ , respectively, by the Cochran–Mantel–Haenszel test, stratified according to whether the patient had undergone nephrectomy and according to geographic region).

In exploratory subgroup analyses using a Cox proportional-hazards model, the salutary effects of temsirolimus alone on overall survival were consistent across the prespecified factors tested, with two exceptions. For the analysis comparing temsirolimus with interferon, we found an interaction of treatment with age ( $P = 0.02$ ) and the baseline serum lactate dehydrogenase level ( $P = 0.008$ ) (Fig. 2). The effect of temsirolimus on overall survival was greater among patients under 65 years of age than among older patients and among patients with a serum lactate dehydrogenase level of more than 1.5 times the upper limit of the normal range than among those with lower levels.

#### ADVERSE EVENTS

Table 3 lists adverse events. Asthenia was most common in the two groups receiving interferon alone or in combination. Grade 3 or 4 asthenia was reported in 11% of patients in the temsirolimus group, in 26% of those in the interferon group ( $P < 0.001$ ), and in 28% of those in the combination-therapy group ( $P < 0.001$ ). The proportions of pa-

tients who reported dyspnea, diarrhea, nausea, or vomiting were similar in the three groups. As compared with patients in the interferon group, mild to moderate rash, peripheral edema, and stomatitis affected more patients who received temsirolimus, either alone or in combination with interferon.

Anemia, neutropenia, and thrombocytopenia were more common in the combination-therapy group than in the interferon group ( $P < 0.001$  for anemia, neutropenia, and thrombocytopenia) or in the temsirolimus group ( $P < 0.001$  for neutropenia and thrombocytopenia, and  $P = 0.002$  for anemia). Hyperglycemia, hypercholesterolemia, and hyperlipidemia were more common in the temsirolimus group and the combination-therapy group, reflecting inhibition of mTOR-regulated glucose and lipid metabolism. Grade 3 or 4 adverse events occurred in 67% of patients in the temsirolimus group, as compared with 78% of patients in the interferon group ( $P = 0.02$ ) and 87% of patients in the combination-therapy group ( $P = 0.02$ ).

Dose reductions and dose delays were less common in the temsirolimus group (Table 4). The different frequencies of adverse events that resulted in dose delays or dose reductions led to different mean relative dose intensities in the three groups. In the interferon group, the mean dose of interferon received over the first 8 weeks of treatment was 30.2 million U per week, or approximately 56% of the maximum planned dose. For the temsirolimus group, the mean weekly dose of temsirolimus was 23.1 mg, or 92% of the planned dose.

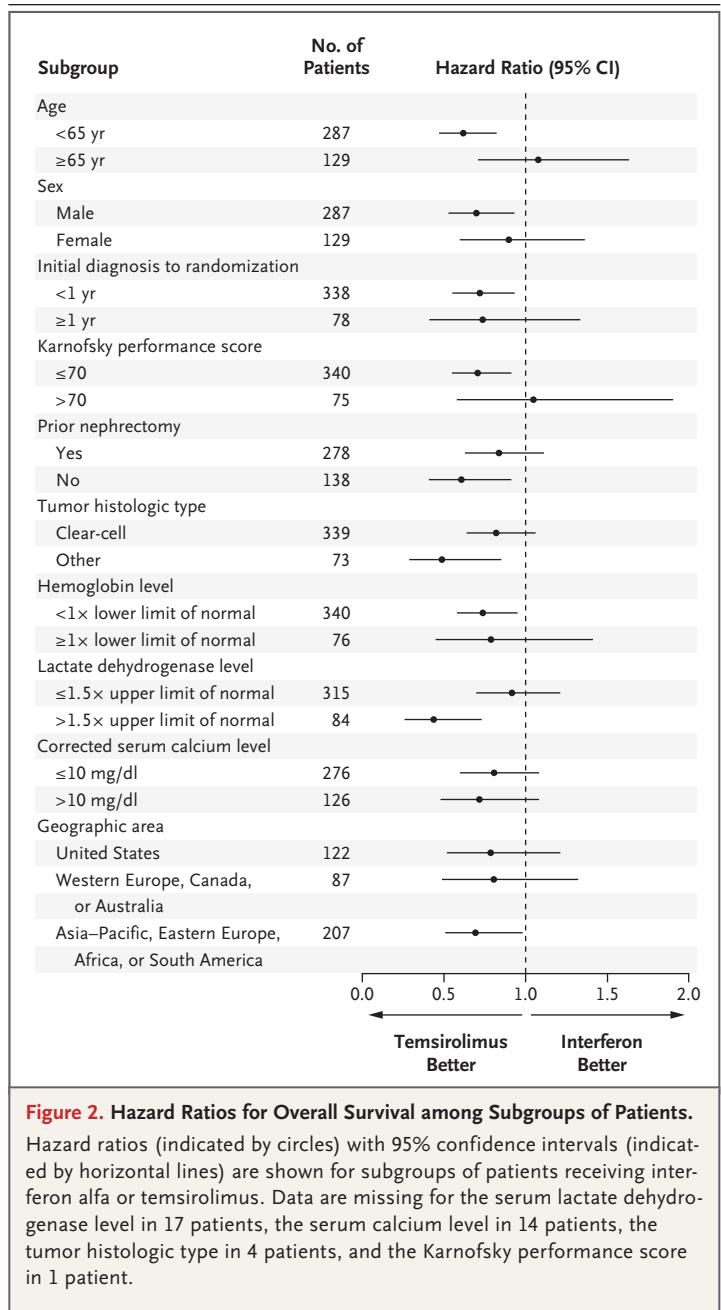
The combination-therapy group received a mean interferon dose of 13.1 million U per week and a mean temsirolimus dose of 10.9 mg per week, or 72% and 73%, respectively, of the planned weekly doses.

## DISCUSSION

This randomized trial compared interferon alone, temsirolimus alone, and a combination of the two drugs for the treatment of newly diagnosed metastatic renal-cell carcinoma. The principal finding was that, as compared with interferon alone, treatment with temsirolimus was associated with a moderate prolongation of overall survival in patients with advanced renal-cell carcinoma and a poor prognosis. The median overall survival in the group given temsirolimus alone was 10.9 months, as compared with 7.3 and 8.4 months in the groups given interferon alfa or combination therapy, respectively. Median progression-free survival times in these three groups were 3.8, 1.9, and 3.7 months, respectively, as determined by the site investigators' assessment, and 5.5, 3.1, and 4.7 months, as determined by independent radiologists. Temsirolimus alone was associated with grade 3 or grade 4 adverse events in fewer patients than was interferon alfa alone. The most common adverse effects of temsirolimus were asthenia, rash, anemia, nausea, dyspnea, diarrhea, peripheral edema, hyperlipidemia, and hyperglycemia. These symptoms were usually manageable with supportive care or a reduction in the drug dose.

Unlike temsirolimus alone, the combination of temsirolimus plus interferon did not improve overall survival. The group that received this combination had the greatest number of patients with grade 3 or 4 adverse events and consequently had more delays and reductions in treatment. The mean dose intensity of temsirolimus was also lower in the combination-therapy group than in the temsirolimus group (10.9 mg vs. 23.1 mg per week). These delays and reductions could explain the failure of the combination therapy to improve overall survival more than interferon alone. It is also possible that the high rate of serious adverse events reduced overall survival in the combination group.

This study involved patients with extensive metastatic disease and multiple adverse prognostic factors. Such patients would be expected to have a shorter survival than patients enrolled in studies of cytokine therapy<sup>2-6,26</sup> or in trials of sunitinib malate or sorafenib.<sup>27,28</sup> Although the definition of poor prognosis varies in published reports, certain features are common to all variants of this category: an interval of less than 1 year from the original diagnosis to the development of metastatic disease, metastases in multiple organs, a low Karnofsky score, anemia, and elevated serum levels of lactate dehydrogenase and calcium.<sup>29</sup> In previous studies, patients with none or only one of these features had a median survival of



**Figure 2. Hazard Ratios for Overall Survival among Subgroups of Patients.**

Hazard ratios (indicated by circles) with 95% confidence intervals (indicated by horizontal lines) are shown for subgroups of patients receiving interferon alfa or temsirolimus. Data are missing for the serum lactate dehydrogenase level in 17 patients, the serum calcium level in 14 patients, the tumor histologic type in 4 patients, and the Karnofsky performance score in 1 patient.

**Table 3. Adverse Events Occurring in at Least 20% of Patients in Any Group.\***

| Adverse Event                                   | Interferon<br>(N=200)         |                 | Temsirolimus<br>(N=208) |                 | Interferon plus<br>Temsirolimus<br>(N=208) |                  |
|---|-------------------------------|-----------------|-------------------------|-----------------|--|------------------|
|   | All<br>Grades                 | Grade<br>3 or 4 | All<br>Grades           | Grade<br>3 or 4 | All<br>Grades                              | Grades<br>3 or 4 |
|   | <i>percentage of patients</i> |                 |                         |                 |  |                  |
| Asthenia  | 64                            | 26              | 51                      | 11              | 62   | 28               |
| Rash  | 6                             | 0               | 47                      | 4               | 21   | 1                |
| Anemia  | 42                            | 22              | 45                      | 20              | 61   | 38               |
| Nausea  | 41                            | 4               | 37                      | 2               | 40   | 3                |
| Anorexia  | 44                            | 4               | 32                      | 3               | 38   | 8                |
| Pain  | 16                            | 2               | 28                      | 5               | 20   | 6                |
| Dyspnea   | 24                            | 6               | 28                      | 9               | 26   | 10               |
| Hyperlipidemia                                  | 14                            | 1               | 27                      | 3               | 38   | 8                |
| Infection                                       | 14                            | 4               | 27                      | 5               | 34   | 11               |
| Diarrhea  | 20                            | 2               | 27                      | 1               | 27   | 5                |
| Peripheral edema                                | 8                             | 0               | 27                      | 2               | 16   | 0                |
| Hyperglycemia                                   | 11                            | 2               | 26                      | 11              | 17   | 6                |
| Cough   | 14                            | 0               | 26                      | 1               | 23   | 2                |
| Hypercholesterolemia                            | 4                             | 0               | 24                      | 1               | 26   | 2                |
| Fever   | 50                            | 4               | 24                      | 1               | 60   | 3                |
| Abdominal pain                                  | 17                            | 2               | 21                      | 4               | 17   | 3                |
| Stomatitis                                      | 4                             | 0               | 20                      | 1               | 21   | 5                |
| Constipation                                    | 18                            | 1               | 20                      | 0               | 19   | 0                |
| Back pain                                       | 14                            | 4               | 20                      | 3               | 15   | 2                |
| Vomiting  | 28                            | 2               | 19                      | 2               | 30   | 2                |
| Weight loss                                     | 25                            | 2               | 19                      | 1               | 32   | 6                |
| Headache  | 15                            | 0               | 15                      | 1               | 22   | 0                |
| Increased creatinine level                      | 10                            | 1               | 14                      | 3               | 20   | 3                |
| Thrombocytopenia                                | 8                             | 0               | 14                      | 1               | 38   | 9                |
| Chills  | 30                            | 2               | 8                       | 1               | 34   | 1                |
| Increased aspartate amino-<br>transferase level | 14                            | 4               | 8                       | 1               | 21   | 4                |
| Neutropenia                                     | 12                            | 7               | 7                       | 3               | 27   | 15               |
| Leukopenia                                      | 17                            | 5               | 6                       | 1               | 31   | 9                |

\* The patients in this analysis did not include those who underwent randomization but received no treatment: seven in the interferon group, one in the temsirolimus group, and two in the combination-therapy group.

about 2 years. By contrast, patients with three or more poor-risk features had a median overall survival of 4 to 8 months.<sup>7-9,29</sup> In our study, the interferon group had a median overall survival of 7.3 months.

Patients with extensive and rapidly progressive disease may be less able to tolerate treatment and may have tumors that are inherently more resistant

to therapy. Accordingly, the moderate efficacy of temsirolimus in advanced disease suggests that the drug might benefit patients with less extensive metastatic renal-cell carcinoma.

Both temsirolimus and sirolimus (rapamycin), its primary metabolite, are potent and specific inhibitors of mTOR. Intravenous administration of temsirolimus raises plasma concentrations of both

**Table 4. Treatment Summary.\***

| Variable                                       | Interferon | Temsirolimus | Interferon plus Temsirolimus |
|--|------------|--------------|------------------------------|
| No. of patients at randomization               | 207        | 209          | 210                          |
| No. of patients treated                        |            |              |                              |
| Interferon                                     | 200        | NA           | 208†                         |
| Temsirolimus                                   | NA         | 208          | 200                          |
| Duration of interferon treatment — wk          |            |              |                              |
| Median   | 8          | NA           | 12                           |
| Range  | 1–124      | NA           | 1–138                        |
| Duration of temsirolimus treatment — wk        |            |              |                              |
| Median   | NA         | 17           | 15                           |
| Range  | NA         | 1–126        | 1–138                        |
| Patients with ≥1 dose reduction — no. (%)      |            |              |                              |
| Interferon                                     | 78 (39)    | NA           | 99 (48)                      |
| Temsirolimus                                   | NA         | 48 (23)      | 59 (30)                      |
| Patients with ≥1 dose delay — no. (%)          |            |              |                              |
| Interferon                                     | 135 (68)   | NA           | 177 (86)                     |
| Temsirolimus                                   | NA         | 137 (66)     | 163 (82)                     |
| Mean dose intensity‡                           |            |              |                              |
| Temsirolimus — mg/wk                           | NA         | 23.1         | 10.9                         |
| Interferon — million U/wk                      | 30.2       | NA           | 13.1                         |
| Reason for treatment discontinuation — no. (%) |            |              |                              |
| Disease progression                            | 115 (58)   | 153 (74)     | 100 (48)                     |
| Adverse event                                  | 29 (14)    | 15 (7)       | 42 (20)                      |
| Symptomatic deterioration                      | 28 (14)    | 14 (7)       | 21 (10)                      |
| Death  | 10 (5)     | 6 (3)        | 17 (8)                       |
| Request by patient                             | 6 (3)      | 8 (4)        | 7 (3)                        |
| Other  | 4 (2)§     | 2 (1)¶       | 6 (3)                        |
| Protocol violation                             | 2 (1)      | 1 (0.5)      | 0                            |

\* NA denotes not applicable.

† This number includes eight patients who did not receive temsirolimus.

‡ The mean dose intensity was the total exposure per week of treatment.

§ The reasons included the patient's loss to follow-up, the investigator's decision, the need for surgery, and the patient's request.

¶ The reasons included disease progression and the investigator's decision.

|| The reasons included the need for a prohibited treatment (radiation therapy), the patient's noncompliance, the investigator's request, a general worsening of the patient's health, and disease progression.

temsirolimus and sirolimus.<sup>20–22</sup> Thus, both moieties probably contribute antitumor activity after the administration of temsirolimus.

The results of this trial point to mTOR as a target for cancer treatment. Since differences in study populations and primary end points in published clinical trials preclude direct comparisons of temsirolimus with other new agents,<sup>27,28</sup> conclusions regarding relative efficacy must await ad-

ditional randomized clinical trials. Nonetheless, the results of this trial suggest the possibility of using temsirolimus as first-line treatment for metastatic renal-cell carcinoma.

Supported by Wyeth Research.

Dr. Hudes reports receiving consulting and lecture fees from Pfizer Pharmaceuticals and consulting fees from Wyeth Pharmaceuticals; Drs. Carducci and Motzer, consulting fees from Wyeth Pharmaceuticals; Dr. Dutcher, consulting and lecture

fees from Novartis, Chiron, Bayer, and Onyx Pharmaceuticals, consulting fees from Wyeth Pharmaceuticals, lecture fees from Pfizer Pharmaceuticals, and research grants from Bayer, Chiron, Genentech, Pfizer, and Wyeth Pharmaceuticals; Dr. Figlin, consulting and lecture fees and research grants from Wyeth Pharmaceuticals; Dr. Kapoor, consulting fees and research grants from Wyeth Pharmaceuticals and research grants from Bayer Pharmaceuticals; Dr. McDermott, consulting fees from Bayer, Onyx, and Genentech Pharmaceuticals and lecture fees from Novartis Pharmaceuticals; and Dr. Schmidt-Wolf, symposium support fees from Wyeth Pharmaceuticals. Mr. O'Toole,

Ms. Lustgarten, and Dr. Moore report being full-time employees of Wyeth Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

We thank the patients and their families and the clinical personnel who participated in this study; the independent data and safety monitoring committee; L.J. Wei of Harvard University for biostatistical analysis; and representatives of Wyeth Research: A. Berkenblit, L. Fahy, L. Galand, and A. Thiele for clinical management; E. Faith and L. Goldberg for clinical programming; S. Kong, Y. Park, and Andrew Strahs for biostatistical analysis; and S. Leinbach for assistance with the preparation of the manuscript.

## APPENDIX

In addition to the authors, the following investigators (listed in alphabetical order) enrolled patients in the Global Advanced Renal-Cell Carcinoma Trial: **Argentina** — R. Bordenave, J. Ibarra, D. Maldonado, C. Martin, M. Tatangelo, J. Zarba; **Australia** — A. Bonaventura, I. Davis, R. De Boer, P. De Souza, H. Gurney, S.-N. Sudarshan, M. Rosenthal; **Canada** — G. Batist, G. Bjarnason, K. Chi, P. Czaykowski, S. Ellard, L. Lacombe, P. Perrotte, C. Prady, M. Reaume, F. Saad, P. Venner, E. Winquist, L. Wood, L. Zibdawi; **Czech Republic** — I. Kocak, J. Prausova; **Germany** — J. Beck, H. Rübber; **Greece** — V. Georgoulas, H. Kalofonos; **Hungary** — M. Baki; **Italy** — M. Bregni, F. Cognetti, L. Gesualdo; **Latvia** — M. Bitina, I. Kudaba, G. Purkalne; **Lithuania** — F. Jankevicius; **the Netherlands** — M. De Groot, P. De Mulder, D. Richel; **Poland** — T. Demkow, T. Dmowski, K. Drosik, A. Jagiello-Gruszfeld, A. Pluzanska, Z. Rusinowska, C. Szczylik; **Russia** — O. Karyakin, B. Komyakov, R. Laslo Dulovich, V. Loubennikov, A. Makhson, B. Matveev, V. Moiseyenko, S. Odintsov, V. Pavlov, I. Rusakov, S. Tjulandin; **Serbia and Montenegro** — D. Donat, S. Radulovic; **Slovakia** — V. Balaz, J. Kliment, J. Mardiak, J. Mikulas; **South Africa** — G. Cohen, K. Maart, P. Ruff; **Spain** — A. Font, J. González Larriba, P. Maroto; **Sweden** — A. Laurell, P. Pisa, K. Stierner; **Taiwan** — J.W.-C. Chang, C.-F. Chiu, M.-J. Huang, W.T.-W. Liu; **Turkey** — M. Basaran, G. Demir; **Ukraine** — G. Bondar, I. Klymenko, A. Lyulko, O. Lyulko, Y. Shparyk; **United Kingdom** — R. Hawkins, M. Sokal, J. White; **United States** — M. Agarwal, R. Amato, P. Benedetto, R. Bukowski, R. Castillo, A. Chakrabarti, G. Chatta, H. Chun, P. Cobb, K. Conlon, B. Curti, T. Dobbs, M. Ernst-off, G. Fumo, G. Geils, J. Gollob, B. Graham, H. Harvey, R. Horns, Jr., B. Kasimis, D. Laber, T. Logan, R. Luyun, G. Mills, D. Minor, D. Nanus, H. Ozer, S. Papish, K. Pendergrass, J. Picus, D. Sahasrabudhe, W. Samlowski, L. Schwartzberg, N. Siddique, W. Smith, N. Tannir, S. Tejwani, J. Thompson, P. Van Veldhuizen, P. Vongkavit, J. Vuky, T. Warr, R. Zon. **Independent Data and Safety Monitoring Committee:** M. Aapro, T. Fleming, J. Kaye, S. Piantadosi, and W. Stadler.

## REFERENCES

- Jemal A, Siegel R, Ward E, et al. Cancer statistics 2006. *CA Cancer J Clin Oncol* 2006; 56:106-30.
- Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon alpha-2a, or both in metastatic renal-cell carcinoma. *N Engl J Med* 1998;338:1272-8.
- Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol* 1995;13:688-96.
- McDermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2005;23:133-41. [Erratum, *J Clin Oncol* 2005;23:2877.]
- Motzer RJ, Murphy BA, Bacik J, et al. Phase III trial of interferon alfa-2a with or without 13-cis-retinoic acid for patients with advanced renal cell carcinoma. *J Clin Oncol* 2000;18:2972-80.
- Aass N, De Mulder HM, Mickisch GHJ, et al. Randomized phase II/III trial of interferon alfa-2a with and without 13-cis-retinoic acid in patients with progressive metastatic renal cell carcinoma: the European Organization for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group (EORTC 30951). *J Clin Oncol* 2005;23:4172-8.
- Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 2002;20:289-96.
- Negrier S, Escudier B, Gomez F, et al. Prognostic factors of survival and rapid progression in 782 patients with metastatic renal carcinomas treated by cytokines: a report from the Groupe Français d'Immunothérapie. *Ann Oncol* 2002;13:1460-8.
- Mekhail TM, Abou-Jawde RM, Boumerhi G, et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. *J Clin Oncol* 2005;23:832-41.
- Schmelzle T, Hall MN. TOR, a central controller of cell growth. *Cell* 2000;103:253-62.
- Fingar DC, Richardson CJ, Tee AR, Cheatham L, Tsou C, Blenis J. mTOR controls cell cycle progression through its cell growth effectors S6K1 and 4E-BP1/eukaryotic translation factor 4E. *Mol Cell Biol* 2004;24:200-16.
- Hudson CC, Liu M, Chiang GG, et al. Regulation of hypoxia-inducible factor 1 $\alpha$  expression and function by the mammalian target of rapamycin. *Mol Cell Biol* 2002;22:7004-14.
- Skotnicki JS, Leone CL, Smith AL, et al. Design, synthesis and biological evaluation of C-42 hydroxyesters of rapamycin: the identification of CCI-779. *Clin Cancer Res* 2001;7:Suppl:3749S-3750S. abstract.
- Harding MW. Immunophilins, mTOR, and pharmacodynamic strategies for a targeted cancer therapy. *Clin Cancer Res* 2003;9:2882-6.
- Hay N, Sonenberg N. Upstream and downstream of mTOR. *Genes Dev* 2004;18:1926-45.
- Yu K, Toral-Barza L, Discafani C, et al. mTOR, a novel target in breast cancer: the effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer. *Endocr Relat Cancer* 2001;8:249-58.
- Thomas GV, Tran C, Mellinghoff IK, et al. Hypoxia-inducible factor determines sensitivity to inhibitors of mTOR in kidney cancer. *Nat Med* 2006;12:122-7.
- Del Bufalo D, Ciuffreda L, Triscioglio D, et al. Antiangiogenic potential of the mammalian target of rapamycin inhibitor temsirolimus. *Cancer Res* 2006;66:5549-54.
- Pantuck AJ, Zeng G, Belldegrun AS, Figlin RA. Pathobiology, prognosis, and targeted therapy for renal cell carcinoma:

- exploiting the hypoxia-induced pathway. *Clin Cancer Res* 2003;9:4641-52.
- 20.** Raymond E, Alexandre J, Faivre S, et al. Safety and pharmacokinetics of weekly intravenous infusion of CCI-779, a novel mTOR inhibitor, in patients with cancer. *J Clin Oncol* 2004;22:2336-47.
- 21.** Hidalgo M, Buckner JC, Erlichman C, et al. A phase I and pharmacokinetic study of temsirolimus (CCI-779) administered intravenously daily for 5 days every 2 weeks to patients with advanced cancer. *Clin Cancer Res* 2006;12:5755-63.
- 22.** Atkins MB, Hidalgo M, Stadler WM, et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol* 2004;22:909-18.
- 23.** Smith II JW, Ko Y, Dutcher J, et al. Phase 1/2 study of intravenous CCI-779 given in combination with interferon- $\alpha$  to patients with advanced renal cell carcinoma. *Proc Am Soc Clin Oncol* 2004;22: Suppl:14S. abstract.
- 24.** Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92:205-16.
- 25.** O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;5:549-56.
- 26.** Atkins MB, Sparano J, Fisher RI, et al. Randomized phase II trial of high-dose interleukin-2 either alone or in combination with interferon alfa-2b in advanced renal cell carcinoma. *J Clin Oncol* 1993;11:661-70.
- 27.** Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356:115-24.
- 28.** Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125-34.
- 29.** Bukowski RM, Negrier S, Elson P. Prognostic factors in patients with advanced renal cell carcinoma: development of an international kidney cancer working group. *Clin Cancer Res* 2004;10:6310S-6314S.

Copyright © 2007 Massachusetts Medical Society.