Sorafenib and Sunitinib in Renal Cell Carcinoma

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The Food and Drug Administration has recently approved sorafenib and sunitinib, two oral multitargeted tyrosine kinase inhibitors, for the treatment of advanced renal cell carcinoma (RCC). Because of the central role of vascular endothelial growth factor (VEGF) in this disease and the activity of VEGF-targeted agents, RCC serves as a unique arena for the evaluation of antiangiogenic agents. In clear cell RCC, mutation or deletion of the von Hippel-Lindau gene is the defining somatic genetic event (1). This result in unopposed activity of the hypoxia-inducible factor signaling complex that regulates the transcription of a number of proangiogenic growth factors, of which VEGF is the best studied. Supporting the essential role of VEGF in the malignant phenotype in RCC, a monoclonal antibody targeted to VEGF exerts its greatest single-agent activity in this disease (2). Sorafenib and sunitinib antagonize VEGF receptor (VEGFR) tyrosine kinases as well as numerous other signaling molecules. The role of these agents as VEGFR inhibitors in RCC is well established; however, their unique spectra of activity deserve additional consideration.

Sorafenib

Preclinical data. Sorafenib, a biaryl urea, is a small molecule tyrosine kinase inhibitor selected in screening experiments against c-Raf (c-Raf IC\(_{50} = 6\) nmol/L), resulting in diminished MEK-1 and ERK-1 phosphorylation (3, 4). Biochemical assays showed the inhibition of multiple tyrosine kinases with a low nanomolar IC\(_{50}\), including B-Raf (22 nmol/L), V599E B-Raf (38 nmol/L), VEGFR-1 (26 nmol/L), VEGFR-2 (90 nmol/L), VEGFR-3 (20 nmol/L), platelet-derived growth factor receptor \(\beta\) (PDGFR; 57 nmol/L), FLT-3 (33 nmol/L), and c-KIT (58 nmol/L; refs. 4–6). Crystallization of sorafenib with wild-type B-Raf and the oncogenic V599E B-Raf showed that the pyridyl ring of sorafenib directly interacts with three amino acids within the ATP adenine binding pocket and that the urea moiety forms several hydrogen bonds with the enzyme (7).

In vitro, sorafenib interrupts ERK phosphorylation in multiple cell lines including cells with mutations in either K-Ras or V599E B-Raf, as well as human umbilical vein endothelial cells and NIH 3T3–VEGFR-2 cells stimulated with VEGF. Similarly, sorafenib inhibited VEGFR-2 autophosphorylation in human umbilical vein endothelial cells, and NIH 3T3–VEGFR-2 cells and PDGFR-autophosphorylation in primary human aortic smooth muscle cells at a concentration of <100 nmol/L (4, 8).

In human xenograft models, treatment with sorafenib at 30 to 60 mg/kg resulted in growth stasis in HT-29, Colo-205, and DLD-1 colon cancer cell lines, as well as the A549 lung cancer cell line, all of which have mutations in KRAS or BRAF. However, in the Colo-205 and A549 tumors, ERK-1/2 phosphorylation was not reduced by sorafenib. Inhibition of vascularization in RENCA murine renal adenocarcinoma, Colo-205, and MDA-MB-231 xenografts occurred even in the absence of RAF inhibition in the tumor itself (9). Taken together, these preclinical studies suggest that tumor growth inhibition by sorafenib is mediated by inhibition of the mitogen-activated protein kinase pathway in some settings, whereas in others, tumor growth inhibition is mediated predominantly by inhibiting angiogenesis via VEGF and PDGF inhibition.

Clinical trials. Four phase I trials of sorafenib, using different schedules, have been reported (10). Treatment cycles lasted 14 days (7 days on/7 days off; ref. 11), 28 days (21 days on/7 days off; ref. 12), and 35 days (28 days on/7 days off; ref. 13). In the fourth and largest phase I trial by Strumberg et al., patients received a starting dose of 50 mg on day 1 of a weekly treatment cycle (14). After an initial period of dose escalation according to a once weekly single-dosing schedule, dose escalation shifted to twice daily (b.i.d.) drug administration. Sixty-nine patients were enrolled in this study, 22 on a noncontinuous dosing schedule and 47 with continuous b.i.d. dosing. Patients on the noncontinuous dosing schedule did not experience any dose-limiting toxicities. Dose-limiting, grade 3 diarrhea and fatigue occurred in three of six patients treated with 800 mg b.i.d. At 600 mg b.i.d., 4 of 14 patients (29%) experienced at least one first cycle dose-limiting skin toxicity; therefore, 400 mg b.i.d. of sorafenib was determined to be the maximum tolerated dose and the recommended phase II dose. Given that the rate of grade 3 toxicity was <33%, and skin toxicities could diminish with continued dosing, it is unclear whether 600 mg twice daily was truly intolerable.

Substantial accumulation in plasma concentrations were observed following multiple b.i.d. administrations. Mean \(t_{1/2}\) ranged from 24 to 38 h. \(C_{\text{max}}\) and area under the curve values were highly variable following single doses of sorafenib from 100 to 400 mg, and multiple doses from 400 to 800 mg. Intake of food before dosing had a minimal effect on pharmacokinetic variables. Phorbol myristate acetate stimulated lymphocytes taken before treatment on day 0, day 2, day 7, and weekly thereafter for at least 6 weeks showed partial inhibition ERK phosphorylation at 200 mg b.i.d. continuous dosing and almost complete inhibition of ERK phosphorylation at 400 mg b.i.d. on day 21 of a continuous dosing schedule.
In a pooled analysis of the sorafenib phase I results, 179 patients were evaluated for safety and efficacy (10). Across all dose levels and schedules, 12% of patients experienced stabilization of previously progressive disease for at least 6 months, and 6% were stabilized for at least 1 year. Analysis of the subset of patients treated close to the recommended phase II dose (300-600 mg b.i.d.) suggested that patients experiencing grade 2 skin toxicity/diarrhea had a longer time to progression compared with patients who did not experience toxicity. However, it is unclear if these toxicities reflect an increase in drug exposure to BAY-43-9006 or unique susceptibility to the drug due to polymorphisms in sorafenib targets.

Based on preclinical models and phase I data showing that the primary benefit of sorafenib was disease stabilization, a phase II study was conducted using a novel randomized discontinuation design in which all patients received study drug (sorafenib, 400 mg b.i.d.) for an initial run-in period, followed by random assignment of patients with disease stabilization to either the study drug or placebo (15). The trial was initially designed to focus on patients with colorectal cancer, while allowing patients with other tumor types to enroll. When responses were observed in patients with RCC, but not colorectal cancer, recruitment was directed to that population. A total of 502 patients were enrolled, with 202 patients having advanced RCC. All patients had Eastern Cooperative Oncology Group performance status 0 or 1, 75% had clear cell RCC and 7% (15 patients) had papillary RCC, 89% had prior nephrectomy, and 76% had previous interleukin 2 or IFN. In patients with RCC, investigator assessment of response (by WHO criteria) after the 12-week run-in determined that 36% of patients had tumor shrinkage by >25%, 34% had stable disease, and 25% had progression at or before week 12. Of note, 4% of patients had an independently confirmed partial response at week 12 (11% by investigator assessment). Of the 15 patients with papillary RCC, there were 2 partial responses and 3 patients with tumor shrinkage of 25% to 49%. At week 12, patients were randomly assigned to receive sorafenib (32 patients) or placebo (33 patients). The primary end point of the study, the percentage of randomly assigned patients who remained progression-free at 12 weeks following random assignment (24 weeks after study entry), was 50% of patients receiving sorafenib versus 18% of patients receiving placebo ($P = 0.0077$). The median progression-free survival (PFS) after randomization was 24 weeks with sorafenib versus 6 weeks with placebo ($P = 0.0087$; hazard ratio, 0.29).

The clinical benefit of sorafenib in advanced RCC has been confirmed in a multicenter, double-blind, randomized phase III trial of sorafenib versus placebo in 903 cytokine-refractory patients (16). Common treatment-related adverse events, of any grade, occurring more frequently in patients treated with sorafenib compared with placebo, included diarrhea (43% versus 13%), rash (40% versus 16%), fatigue (37% versus 28%), hand-foot syndrome (30% versus 7%), and hypertension (17% versus 2%). Frequent grade 3/4 toxicities included hand-foot reaction (6% versus 0%), hypophosphatemia (13% versus 3%), and elevated lipase (12% versus 7%). Three percent of patients in both arms discontinued therapy due to an adverse event. In the sorafenib and control arms, dose interruption due to an adverse event occurred in 21% and 6% of patients, and doses were reduced in 13% and 3% of patients, respectively. The investigator-assessed response rate according to Response Evaluation Criteria in Solid Tumors (RECIST) standards was 10% versus 2% in favor of sorafenib (2% versus 0% with central review), with 76% versus 25% of patients having some reduction in the burden of disease. The median PFS, according to independent review, was 5.5 months for sorafenib versus 2.8 months for placebo ($P < 0.001$) and benefit was present in all subgroups based on age (>65 years, Motzer score, prior interleukin 2, location of metastases and time from diagnosis, >1.5 years for diagnosis). Although the primary end point of this trial was intended to be overall survival, the magnitude of benefit in PFS prompted an alteration in the conduct of the study, with placebo-treated patients being offered cross-over treatments to sorafenib. Based on a planned interim analysis at 220 deaths, that there was an estimated 39% improvement in survival for patients receiving sorafenib versus those receiving placebo ($P = 0.02$; hazard ratio, 0.72). However, the median overall survival for sorafenib was not reached at the time of this analysis and the threshold for statistical significance of the interim analysis of survival was not achieved. The final survival analysis will be conducted when 540 events have occurred, but will undoubtedly be influenced by the cross-over effect.

**Sunitinib**

**Preclinical data.** Sunitinib is a selective inhibitor of the class III and V receptor tyrosine kinases, including the PDGFRs, c-KIT, FLT-3, and the VEGFRs. In biochemical assays, sunitinib exhibited competitive inhibition against VEGFR-2 and PDGFRβ, with a $K_i$ of 9 and 8 nmol/L, respectively (17, 18). In cellular inhibition assays, sunitinib inhibited VEGF-dependent VEGFR-2 phosphorylation and PDGF-dependent PDGFRβ phosphorylation with $IC_{50}$ values of 10 nmol/L for both receptor tyrosine kinases (17). In addition, sunitinib inhibited VEGF and basic fibroblast growth factor–induced proliferation of human umbilical vein endothelial cells.

In human xenograft models, sunitinib induced regression in HT-29 and Colo-205 tumors. (17). Complete and durable regression occurred in six out of eight mice bearing large A431 (epidermoid) tumors. Additionally, in some models, such as luciferase-expressing PC-3 prostate tumor transplants, treatment with sunitinib caused decreased fluorescence and growth stasis, but no reduction in tumor size. In SF763T glioma tumors, sunitinib treatment resulted in an ~40% reduction in microvesSEL density. Oral administration of sunitinib to mice bearing Colo-205 tumors that do not express PDGFRβ lead to decreased phosphorylation of this receptor, indicating that decreased phosphorylation was occurring in pericytes, and stromal tissue. Thus, sunitinib demonstrates the ability to reduce tumor cell viability and inhibit angiogenesis, even when tumors do not express receptor tyrosine kinases in the spectrum of activity of sunitinib. In animal experiments designed to determine the target plasma concentration of sunitinib, the minimum plasma concentration required to inhibit receptor phosphorylation was concluded to be 100 ng/mL. Furthermore, this concentration had to be maintained for at least 12 h on a daily dosing regimen for efficacy to be maintained.

**Clinical trials.** In the phase I trial of sunitinib in patients with advanced solid tumors, the recommended phase II dose was 50 mg daily for 4 weeks, followed by 2 weeks off treatment in 6-week cycles (19). In this study, body surface area dosing...
was initially used, however, pharmacokinetic analyses revealed that normalizing for body surface area did not reduce the variability in exposure and flat dosing was subsequently employed. Dose-limiting toxicities of fatigue, hypertension, and skin toxicity were observed at doses ≥75 mg/d, but generally resolved completely during the 2-week treatment break. Sunitinib had a long $t_{1/2}$, ranging from 41 to 86 h. The $C_{\text{max}}$ occurred 5 h after administration and accumulation of sunitinib over time was observed. Doses of 50 mg per day led to plasma trough concentrations generally ranging from 50 to 100 ng/mL, whereas patients experiencing dose-limiting toxicities had plasma trough concentrations of >100 ng/mL. Serum VEGF concentrations tended to increase during the 28-day treatment, whereas mean sVEGFR-2 levels decreased. Of note, sunitinib was the first VEGF-targeted therapy to be developed with intermittent drug exposure.

Based on partial responses seen in patients with RCC in the phase I trial, a multicenter phase II study of sunitinib in 63 patients and a second “confirmatory” phase II study in 106 patients was undertaken in patients who progressed on one previous cytokine therapy (20, 21). In both studies, sunitinib was given 50 mg daily in the “4 weeks on/2 weeks off” schedule. The second trial was limited to patients with clear cell RCC. Tumor responses assessed using RECIST standards were similar in the two trials (40% and 43% partial response rate by investigator assessment, 34% by independent review of trial 2 results), with one complete response in the second trial. In pooled results from 168 patients, the partial response rate was 42%, the stable disease rate (≥3 months) was 24%, and 34% of patients progressed or had stable disease for <3 months. Median PFS in the combined analysis was 8.2 months (95% confidence intervals, 7.8-10.4). Median PFS in patients with stable disease of 3 months or longer, it was 7.9 months. The median trough sunitinib concentration in this trial was 84.3 ng/mL, with no accumulation of drug across dosing cycles. In study 1, VEGF-A and placental growth factor (PIGF) levels increased from days 1 to 28, whereas sVEGFR-2 levels decreased. A decrease in left ventricular ejection fraction (LVEF) was noted in 8 out of 106 patients (4.7%) in the second phase II RCC study. In the first study, 35% of patients had their dose reduced while on treatment for asymptomatic hyperlipasemia, hyperamylasemia, or significant fatigue. Recently, interim results were reported for a randomized phase III trial of sunitinib (50 mg/d for 4 out of 6 weeks versus IFN; titrated up to 9 million units thrice a week) in patients with previously untreated, metastatic, clear cell RCC (22). Three hundred and seventy-five patients were randomized to each arm. The primary end point of the study, median PFS, was 11 months for sunitinib (10-12) versus 5 months for IFN (hazard ratio, 0.42; $P < 0.001$; refs. 4-6) as assessed by independent central review. Median overall survival was not reached for either arm at the time of the analysis. The investigator-assessed response rate was 37% with sunitinib and 9% with IFN (31% versus 6% with central review). Common treatment-related adverse events of any grade (for sunitinib compared with IFN) were fatigue (51% versus 51%), diarrhea (53% versus 12%), nausea (44% versus 33%), stomatitis (25% versus 2%), hypertension (24% versus 1%), hand-foot syndrome (20% versus 1%), and ejection fraction decline (10% versus 3%). Frequent grade 3/4 toxicities included fatigue (7% versus 12%), diarrhea (5% versus 0%), hypertension (8% versus 1%), hand-foot syndrome (5% versus 0%), neutropenia (12% versus 7%), thrombocytopenia (8% versus 0%), and elevated amylase (5% versus 3%). In the sunitinib and IFN arms, dose interruption due to an adverse event occurred in 38% and 32% of patients, and doses were reduced in 32% and 21% of patients, respectively. However, patients in the sunitinib group reported a significantly better quality of life than did patients in the IFN-α group using validated questionnaires.

In addition to the toxicities reported above, evaluation of safety data from trials of sunitinib in gastrointestinal stromal tumor and RCC suggests an association between treatment with sunitinib and the development of treatment-related hypothyroidism, potentially explaining some cases of sunitinib-induced fatigue. In patients with gastrointestinal stromal tumor and normal thyroid-stimulating hormone at baseline, development of abnormal serum thyroid-stimulating hormone concentrations whereas being treated with sunitinib was documented in 26 of 42 patients (62%; ref. 23). Furthermore, the risk of developing hypothyroidism seemed to correlate with the duration of exposure to sunitinib. Although 4 out of 22 (18%) patients taking sunitinib for 36 weeks developed hypothyroidism, 9 out of 10 (90%) patients treated for more than 96 weeks with sunitinib developed increased levels of thyroid-stimulating hormone. The mean time to development of hypothyroidism was 50 weeks. In patients with RCC treated with sunitinib, who underwent thyroid function testing, 56 out of 66 (85%) of patients had one or more thyroid function test abnormalities, which developed after a median of two cycles (24). Whether these findings result from sunitinib inducing antithyroid immunity, impairing thyroid vascularization, or interfering with the normal physiologic function of VEGF in thyroid homeostasis, and the extent to which these findings are unique to sunitinib versus sorafenib, remains to be clarified.

Decreased cardiac ejection fraction has also been observed in patients treated with sunitinib. As noted above, in the phase III trial of sunitinib versus IFN, a decrease in LVEF to below the lower limit of normal were seen in 10% of patients receiving sunitinib and in 3% of patients receiving IFN. In the gastrointestinal stromal tumor-randomized trial of sunitinib versus placebo, identical rates of decreased LVEF were seen in the treatment and control groups (25). In both trials, a grade 3 decrease in LVEF to <40% was rare, occurring in ~2% of patients. In most cases, decreased LVEF either recovered spontaneously or with dose reduction of sunitinib and/or cardiac medications such as antihypertensive or diuretic medications (26). Ongoing studies such as the Eastern Cooperative Oncology Group trial of adjuvant sunitinib, sorafenib, or placebo in high-risk RCC, will prospectively evaluate the incidence of LVEF decline in these two receptor tyrosine kinase inhibitors.

**How are Sunitinib and Sorafenib Different?**

Although the recent and contemporaneous approval of two multitargeted tyrosine kinase inhibitors that both seem to alter the natural history of RCC (improved PFS with first line sunitinib and after cytokine therapy for sorafenib) tempts one to lump these two drugs together, this approach may obscure the differences that determine how best to use these drugs in the control (if not yet the cure) of metastatic RCC and other
sorafenib, the dissociation constants for VEGFR-2 and PDGF note, using this standard assay to compare sunitinib and may result in different spectrums of activity and/or toxicity. Of dependent protein kinases is not yet known, yet these differences targeting 'off' kinases such as JAK1, KIT, and the calcium/calmodulin-dependent kinases. The clinical importance of inhibiting 'off compounds and immobilized kinase ligands compete for binding to kinase domains, expressed as fusions to the T7 bacteriophage (27). Bound bacteriophage is then quantified with quantitative PCR. In this assay, sunitinib bound 73 kinases in addition to VEGFR-2, whereas sorafenib bound 40 additional kinases. The clinical importance of inhibiting ‘off target’ kinases such as JAK1, KIT, and the calcium/calmodulin-dependent protein kinases is not yet known, yet these differences may result in different spectrums of activity and/or toxicity. Of note, using this standard assay to compare sunitinib and sorafenib, the dissociation constants for VEGFR-2 and PDGF were 0.23 versus 93 nmol/L and 0.21 versus 41 nmol/L, respectively, implying a significant difference in \textit{in vitro} potency (see Fabian et al. [27]; Supplementary Table S4). Kinase families: TK, nonreceptor tyrosine kinases; RTK, receptor tyrosine kinases; TKL, tyrosine kinase-like kinases; CK, casein kinase family; PKA, protein kinase A family; CAMK, calcium/calmodulin-dependent kinases; CDK, cyclin-dependent kinases; MAPK, mitogen-activated protein kinases; CLK, CDK-like kinases. The kinase dendrogram was adapted from Fabian et al. (27) after Manning et al. (45), and is reproduced with permission from \textit{Nature Biotechnology}, \textit{Science}, and \textit{Cell Signaling Technology}, Inc.\textsuperscript{3}

As previously noted, sorafenib, unlike sunitinib, is a potent inhibitor of Raf kinase, the downstream target of Ras in the mitogen-activated protein kinase. Raf has been identified as a mediator of cellular proliferation, differentiation, adhesion, migration, metastasis, and survival pathways (28, 29). In RCC, activated, phosphorylated Raf-1 was identified in 6 of 11 (55%) tumors (30), although no activating BRAF mutations were identified in a series of RCCs (31). Furthermore, Ras, the upstream target of Raf has only been identified as oncogenic in 10% of RCCs (32), suggesting that Raf in RCC is predominantly activated by increased levels of ligands for growth factor receptor tyrosine kinases such as transforming growth factor-α (29). Unfortunately, whereas model systems clearly suggest an important role for transforming growth factor-α and its receptor EGFR in the pathogenesis of RCC (33, 34), the clinical importance of inhibiting the EGFR pathway has been called into question by a recent trial in which the EGFR inhibitor erlotinib combined with the VEGF inhibitor bevacizumab did not add to the efficacy of bevacizumab alone (35). Therefore, it remains unclear if Ras pathway inhibition has a direct antitumor effect in RCC.

The importance of RAF-MEK-ERK signaling in tumor angiogenesis has been shown in a variety of experimental systems (36–38) and dominant-negative Raf targeted to the neovascularature of tumors induced endothelial apoptosis and inhibited tumor growth (39). Recently, sorafenib, was shown to cause a significant reduction in endothelial cell p-ERK expression in K1735 murine melanomas (in which VEGF is not the mediator of angiogenesis), as well as RENCA renal tumors and Colo-205 cancers. Sorafenib-treated blood vessels also had decreased endothelial cell proliferation as measured by Ki-67, and increased endothelial cell apoptosis, as measured by terminal nucleotidyl transferase–mediated nick end labeling staining (40). As the authors note, however, down-modulation of p-ERK would be expected if VEGFR-2, Raf, or both were targeted by sorafenib in endothelial cells.

At this point, it remains unclear how resistance to sunitinib or sorafenib develops. One can speculate that if sorafenib targets endothelial cell Raf directly rather than through VEGFR-2 inhibition, it is possible that sorafenib may be able to overcome resistance to VEGFR-2 inhibition occurring through up-regulation of VEGF, or other angiogenic factors signaling through the Raf pathway. This is currently a critical question as there is no data to guide to sequential use of these therapies.

Clinically, there are differences between these two medications, in variables such as toxicity (lower grade 3 toxicity rate with sorafenib and fewer dose modifications in the phase III trial), response rate (higher objective response rate with sunitinib, which may be important for patients with bulky and symptomatic disease), and schedule (interrupted dosing for sunitinib versus continuous for sorafenib). On this last point, the first preliminary report on sunitinib administered continuously versus sorafenib in RCC compared response rates, progression-free survival, and toxicity (30). The sunitinib group showed a 4-month median progression-free survival compared with 2 months for sunitinib, but with a lower grade 3 toxicity rate (27% compared with 43%). On the other hand, toxicities with sorafenib were less severe and more manageable (22).

\textsuperscript{3}http://www.cellsignal.com/
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The preliminary objective response rate was less than half the rate reported in the phase II and phase III trials with 50 mg on the 4 days on/2 days off schedule. It is not clear whether progression-free survival or overall survival would be negatively affected by continuous dosing, and even the apparently inferior response rate would require validation in future trials. Nonetheless, this intriguing result suggests that intermittent dosing may maximize response rate. This is certainly counterintuitive for agents that are predominantly antiangiogenic and mandates more thorough exploration of this issue.

To date, neither sorafenib nor sunitinib have been extensively evaluated with patients with papillary or chromophobe RCC. In the phase II trials of sunitinib, &lt;5% of patients had non–clear-cell histologies and separate reporting of activity in this subgroup has not occurred. In the phase III trials of sunitinib and sorafenib, patients with non–clear cell histology were specifically excluded. In the phase II trial of sorafenib, a cohort of patients with papillary RCC were included, as were a very small number of patients with chromophobe RCC. As summarized above, activity was clearly observed in the papillary RCC subset, albeit in a small number of patients. Dedicated phase II trials in papillary RCC are currently being conducted for each agent.

The nearly simultaneous emergence of sorafenib, sunitinib, bevacizumab, and temsirolimus as therapies with established clinical benefit in RCC has set the stage for expedient investigations of targeted therapy combinations. Bevacizumab, a monoclonal antibody that binds and depletes secreted VEGF, is currently being conducted for each agent. Although activity was clearly observed in the papillary RCC subset, it may be a particularly rational therapy to combine with sorafenib or sunitinib given that the increase in serum VEGF induced both of those agents.

Temsirolimus, a specific inhibitor of the mammalian target of rapamycin, seems to have a potentially unique mechanism of action. There is evidence that mammalian target of rapamycin inhibition is directly toxic to RCCs (42). Furthermore, hypoxia-inducible factor 1α expression is regulated by the phosphoinositol-3-kinase pathway and is inhibited by mammalian target of rapamycin inhibition (43, 44). Thus, either bevacizumab or temsirolimus are rationally targeted agents to be combined with sorafenib and sunitinib. Phase I trials investigating each combination are under way. A randomized phase II trial (E2804) is planned to compare to the following combinations: sorafenib with bevacizumab, sorafenib with temsirolimus, and bevacizumab with temsirolimus. The purpose of these trials will be to select a combination regimen to test against the best available single-agent therapy in a subsequent phase III trial.

At the present time, the relative benefit of sorafenib and sunitinib for patients with metastatic RCC has not been compared directly. There is a striking similarity in the reported percentage of patients who experienced some degree of tumor regression in the context of phase II and phase III trials (roughly 75%). An Eastern Cooperative Oncology Group phase III trial, with patients randomized to sunitinib versus sorafenib versus placebo in the adjuvant setting is ongoing, and may point to the relative clinical efficacy of these two agents in the future. At the current time, however, fundamental questions remain unanswered regarding the mechanisms of action of these two drugs and their optimal utilization in the clinic. Clinical trials designed to answer molecular questions using neo-adjuvant therapy, serial biopsies, or novel techniques such as evaluation of circulating tumor cells may help to define therapy of RCC in the years to come.

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