Targeted Therapy for Metastatic Renal Cell Carcinoma: A Home Run or a Work in Progress?

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By Brian I. Rini, MD [2] and Ronald M. Bukowski, MD [3]

Recent advances in the understanding of the biology of renal cell carcinoma (RCC) have been translated into clinical treatment options in metastatic disease.

ABSTRACT: Recent advances in the understanding of the biology of renal cell carcinoma (RCC) have been translated into clinical treatment options in metastatic disease. The introduction of targeted therapy against the vascular endothelial growth factor (VEGF) pathway and related elements has produced robust clinical effects, exceeding those of historical treatment options. Sunitinib (Sutent) and bevacizumab (Avastin) plus interferon have established roles in the initial treatment of metastatic RCC. Sorafenib (Nexavar) is established for cytokine-refractory RCC and is being explored in other settings. Temsirolimus (Torisel) is the only agent to extend overall survival to date, although this finding has been restricted to a poor-risk population. Several clinical questions have thus emerged in regard to the optimal timing, type, and sequence of targeted therapy in metastatic RCC. Novel agents targeting the VEGF or alternative pathways have also emerged and are beginning to undergo clinical testing.

The medical management of metastatic renal cell carcinoma (RCC) has undergone a transformation in recent years. Initial attempts at treatment with hormonal or chemotherapeutic agents produced little success. The historical standard of cytokine immunotherapy, including interleukin (IL)-2 (Proleukin) and interferon (IFN)-alpha, resulted in limited clinical benefit in unselected cohorts. More recently, systemic therapy targeted at the vascular endothelial growth factor (VEGF) protein and related pathway elements has produced robust clinical effects in metastatic RCC, leading to regulatory approval of sorafenib (Nexavar), sunitinib (Sutent), and temsirolimus (CCI-779, Torisel), an inhibitor of the mammalian target of rapamycin (mTOR). Bevacizumab (Avastin) has also demonstrated antitumor activity in metastatic RCC and is awaiting regulatory approval in the United States.

It is useful to review the existing data from each of these approaches to formulate an overall management strategy of metastatic RCC patients. Further, we will discuss ongoing investigative efforts including sequencing, combination therapy and novel agents.

Historical Perspective

Systemic anticancer agents such as medroxyprogesterone acetate and cytotoxic chemotherapy were initially applied to metastatic RCC patients. These agents produced minimal objective response rates of approximately 2% to 5%.[1-4] While symptom palliation can be observed in some patients, the benefit for the entire cohort of RCC patients is extremely low. Despite combination chemotherapy regimens resulting in slightly higher response rates, such regimens are not in routine use pending further study of novel agents or additional patient selection efforts.

The immunogenic nature of RCC and the lack of benefit from chemotherapy and hormone therapy resulted in the clinical application of immunotherapeutic cytokines. Two phase III randomized trials have examined the benefit of high-dose IL-2 and low-dose cytokine (IL-2 monotherapy or IL-2 plus IFN-alpha) regimens (Table 1).[5,6] Both studies demonstrated an objective response rate advantage for the high-dose IL-2 arms, without any difference in disease-free or overall survival. Taken together, these data suggest that high-dose IL-2 has a higher overall and complete response rate compared with low-dose cytokines, with the majority of benefit realized in patients who experience a durable complete response. The limited benefit, however, precluded demonstration of a disease-free or overall survival advantage with high-dose IL-2 for the entire cohort. Further, the lack of applicability of high-dose IL-2 to the broad RCC population has dampened enthusiasm for this approach. TABLE 1
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Low-dose IFN-alpha monotherapy has also been investigated (Table 1). A meta-analysis that reviewed 53 randomized controlled trials with IL-2 or IFN-alpha in metastatic RCC provides the most comprehensive view.[7] Four trials (N = 644) randomized patients to IFN-alpha vs a non–IFN-alpha control arm. The weighted median survival improvement with IFN-alpha treatment vs the control group was 3.8 months ($P = .007$), with an odds ratio for death at 1 year of 0.56 for IFN-alpha (95% confidence interval = 0.40–0.77). The investigators found no evidence of a dose-response relationship and no correlation between response rate and overall survival. Despite multiple attempts, no prospective randomized trial has demonstrated a benefit to adding any additional cytokine/immunotherapeutic or noncytokine agent to cytokine monotherapy, with the notable exception of IFN-alpha plus bevacizumab trials.

The role of cytokine therapy in metastatic RCC is currently evolving and unclear. As noted above, cytokine monotherapy is of modest benefit in unselected populations, but select patients should be considered for high-dose IL-2 therapy, solely on the basis of the small but real chance of a durable complete response. Whether or not this durable complete response benefit is preserved when high-dose IL-2 is given after targeted therapy is not clear at present. Current investigative efforts are appropriately focused on additional patient selection efforts and combination therapy. For example, tumors expressing carbonic anhydrase IX (CAIX, also called G250) have been associated with a higher rate of objective response to IL-2 in retrospective analyses, and further prospective trials are ongoing.[8,9] In addition, based on nonoverlapping mechanisms of action, cytokines are being investigated in combination with targeted therapy, as discussed below.

Targeted Therapy

The premise of targeted therapy in all oncologic endeavors is the fundamental reliance of tumor cells on given biologic pathways that drugs can be designed to disrupt. A growing understanding of the underlying molecular biology of RCC has established the VEGF and mTOR pathways as relevant therapeutic targets.

The pathogenesis of RCC was elucidated by the discovery of the von Hippel-Lindau (VHL) gene, which is named for the familial cancer syndrome in which it is implicated.[10] VHL is a tumor-suppressor gene in which biallelic gene inactivation promotes a tumor phenotype. One allele is inactivated through a deletion (also known as loss of heterozygosity) observed in over 90% of sporadic clear cell RCC cases.[11,12] The remaining VHL allele can be inactivated either through a gene mutation (approximately 50% of clear cell RCC[13,14]) or through gene silencing by methylation (approximately 5% to 10% of cases).[15,16])

Under normal conditions, VHL encodes a protein that targets a crucial transcription factor called hypoxia-inducible factor (HIF) for proteolysis.[17] As a result of the VHL gene inactivation, a defective VHL protein is produced and HIF is not subject to proteolysis and inactivation. Activated HIF then translocates into the nucleus and leads to the transcription of a variety of genes that play a central role in tumor progression. Transcription genes include VEGF,[18] platelet-derived growth factor (PDGF),[19] transforming growth factor (TGF)-alpha,[20] and basic fibroblast growth factor (bFGF). Clinical testing has identified the VEGF protein and its receptor (VEGFR) as the most relevant targets in anti-RCC therapy.

Sunitinib

Sunitinib is a small-molecule inhibitor of the tyrosine kinase portion of VEGFR and related receptors. Updated data from the initial phase II trials of sunitinib in metastatic RCC patients (N = 169) who had failed prior cytokine-based therapy demonstrated an investigator-assessed pooled objective response rate of 45%, a median duration of response of 11.9 months, and median progression-free
A phase III trial in untreated, metastatic RCC patients (N = 750) of sunitinib vs IFN-alpha demonstrated a significant advantage in objective response rate (39% vs 8%, \( P < .000001 \)) and PFS (11 vs 5 months, \( P < .000001 \)) for sunitinib-treated patients (Table 1).[22] Baseline clinical features predictive of improved PFS at 12 months in sunitinib-treated patients identified Eastern Cooperative Oncology Group (ECOG) performance status 0, time from diagnosis \( \geq 1 \) year and corrected serum calcium \( \leq 10 \) mg/dL as favorable characteristics.[22] Based on these data, sunitinib has emerged as a front-line standard of care in metastatic RCC. This drug is notable for a superior objective response rate compared to other agents, balanced against toxicity including fatigue, hand-foot syndrome, and diarrhea. Final analysis of the survival data from this trial is pending.

**Sorafenib**

Sorafenib is a small-molecule inhibitor of VEGFR and related receptors in addition to inhibition of an intracellular-signaling enzyme, raf kinase. A phase III trial of sorafenib randomized 900 treatment-refractory metastatic RCC patients to sorafenib at 400 mg twice daily or placebo. A PFS advantage in the treatment arm was observed (5.5 vs 2.8 months, \( P < .000001 \); Table 1).[23] Although overall survival was similar between the two arms (17.8 vs 15.2 months, \( P = .15 \)), a preplanned analysis demonstrated improved survival with sorafenib after the censoring of placebo patients who crossed over to the sorafenib arm (17.8 vs 14.3 months, \( P = .03 \)).[24] It is likely for this trial and other phase III trials that patient crossover to active therapy may obscure the overall survival benefit of targeted therapy in a single trial. The phase III data contrast somewhat with the results of a smaller, randomized phase II study of sorafenib vs IFN-alpha in 189 previously untreated metastatic RCC patients. In this smaller trial, median PFS was 5.7 months with sorafenib vs 5.6 months with IFN-alpha.[25] The reason for the lack of significant effect vs IFN-alpha in the front-line setting is not entirely clear but may result from weaker inhibition of VEGFR compared to sunitinib. Although there may be patients in whom sorafenib would be the preferred initial agent, for example, due to toxicity profile, sorafenib use has moved toward second-line and later therapy. Investigators need to identify the phenotype of patients in whom sorafenib is the preferred initial treatment.

**Bevacizumab**

Bevacizumab is a monoclonal antibody that binds and neutralizes circulating VEGF protein. The activity of this agent in RCC was initially identified by small randomized trials.[26,27] More recently, two multicenter international studies have established bevacizumab-based therapy as robust in the front-line setting.[28,29] The AVOREN trial randomized 649 untreated patients with metastatic RCC to treatment with IFN alfa-2a (Roferon-A) plus placebo infusion or to IFN alfa-2a with bevacizumab at 10 mg/kg IV every 2 weeks. This trial demonstrated a significant difference in favor of the bevacizumab-containing arm for objective response rate (31% vs 13%, \( P < .0001 \)) and PFS (10.2 vs 5.4 months, \( P < .0001 \)). The second trial, conducted through the Cancer and Leukemia Group B (CALGB), was nearly identical in design, with the exception of using IFN alfa-2b (Intron A) instead of IFN alfa-2a, lacking a placebo infusion, and not requiring prior nephrectomy. This trial also demonstrated a significant difference in favor of the bevacizumab-containing arm for objective response rate (25% vs 13%, \( P < .0001 \)) and PFS (8.5 vs 5.2 months, \( P < .0001 \)). The contribution of IFN-alpha to the antitumor effect of this regimen, especially when balanced against increased toxicity, is unclear, although preliminary results indicate a longer PFS and higher response rate than expected with bevacizumab monotherapy.[27] Based on these findings, regulatory approval of bevacizumab-based therapy in advanced RCC has been granted in Europe and is expected in the United States, and it is likely that bevacizumab-based therapy will join sunitinib as a front-line standard of care. Although the response rate is lower than that seen with sunitinib, bevacizumab is very well tolerated day-to-day and is familiar to community oncologists given its common use in colorectal and lung cancers.

**Temsirolimus**

Temsirolimus is an inhibitor of mTOR, a molecule implicated in multiple tumor-promoting intracellular signaling pathways. Regulation of mTOR pathway activation is mediated through a
series of complex signaling interactions linking growth factor receptor signaling and other cell stimuli, phosphatidylinositol 3-kinase (PI3K) activation, and activation of the Akt/PKB pathway. mTOR phosphorylates and activates p70 S6 kinase (p70S6K), leading to enhanced translation of certain ribosomal proteins and elongation factors. This process leads to—among other effects—the production of HIF-1 alpha, which regulates the transcription of genes that stimulate cell growth and angiogenesis, including VEGF. The second major mTOR effect is on the 4E binding protein-1 (4E-BP1) and eukaryotic initiation factor-4 subunit E (eIF-4E) complex, promoting dissociation of this complex and allowing eIF-4E to stimulate an increase in the translation of mRNAs that encode cell-cycle regulators such as c-myc, cyclin D1, and ornithine decarboxylase.

Retrospective analysis of a prior phase II trial in treatment-refractory metastatic RCC suggested that antitumor activity was more pronounced in a poor-risk subset.[30] A randomized phase III trial was subsequently conducted in patients with metastatic RCC and three or more adverse risk features as defined by the following: Karnofsky performance status < 80%, lactate dehydrogenase > 1.5 × laboratory upper limit of normal, hemoglobin < laboratory lower limit of normal, serum calcium corrected for albumin > 10 mg/dL, time from first diagnosis of RCC to start of therapy < 1 year, plus a sixth factor, ie, three or more metastatic sites identified as prognostic in a separate analysis.[31,32] A total of 626 patients were randomized to temsirolimus at 25 mg IV weekly vs IFN-alpha at 18 MU three times per week vs temsirolimus at 15 mg IV weekly plus IFN-alpha at 6 MU three times per week.

Patients treated with temsirolimus had a statistically longer overall survival than IFN-alpha monotherapy patients (10.9 vs 7.3 months, \( P = .0069 \); Table 1).\[33\] The investigators also found a progression-free survival benefit from temsirolimus monotherapy vs IFN-alpha (median = 3.8 vs 1.9 months, \( P < .0001 \)). There was no survival advantage to the combination-therapy arm over IFN-alpha monotherapy, perhaps due to the lower dose of temsirolimus, which may have been inadequate for mTOR inhibition.

These data led to US Food and Drug Administration approval of temsirolimus for advanced RCC on May 31, 2007, and validated mTOR as a relevant therapeutic target in RCC, at least in the subset of patients with multiple adverse-risk features. This agent is being used frequently in patients who have failed prior therapy, including prior VEGF-targeted therapy, for whom no safety or efficacy data is yet available. The utility of this agent in patients who do not meet the poor-risk criteria of the phase III trial awaits further study.

**Management Strategies for Metastatic RCC Patients**

Given the availability of multiple treatment options, each with a slightly different profile of risk and benefit, there are currently several options for initial therapy. The choice of treatment requires appreciation of the risks and benefits of the agents discussed as well as knowledge of the limitations of the current data. The goal for every metastatic RCC patient upon presentation is to maximize overall therapeutic benefit, delaying for as long possible a life-threatening burden of disease while maximizing quality of life and patient convenience. This translates into selecting the treatment with the optimal risk-benefit ratio for a given patient, while realizing that limited criteria exist to predict response to a given agent and that multiple sequential treatments are ultimately likely to be pursued for most patients.

**When Should Systemic Therapy Be Started?**

Although several active agents are now available for metastatic RCC, their inability to produce durable complete responses necessitates chronic therapy in the majority of patients. Therefore, benefits must be weighed against the overall burden of treatment, including toxicity, time commitment, and cost. A subset of metastatic RCC patients has low-volume, slow-growing disease. For these patients, the overall goal of controlling tumor burden and maximizing quality of life may be achieved more successfully by not initiating immediate systemic therapy.

Evidence suggests that treatment benefit is preserved even if therapy is delayed. For example, Ratain et al reported on 28 patients who were randomized to placebo on the sorafenib randomized discontinuation trial, where sorafenib was readministered upon disease progression.[34] These patients continued on sorafenib until further progression for a median of 24 weeks, identical to the PFS for patients initially randomized to continue sorafenib. These data suggest that some asymptomatic patients can have treatment delayed without compromising the ability to achieve subsequent clinical benefit to therapy.

This critical question of whether a given agent offers identical clinical benefit after a period of
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observation will require prospective study. This treatment delay could also provide a window for exploring investigational therapy with low toxicity.

Which Agent First?

All the targeted therapies noted above have demonstrated benefit in a phase III setting vs either interferon monotherapy or placebo. None of these agents have been directly compared to one another, and thus definitive answers to this question are not readily available. As noted above, patients are likely to be treated with multiple agents in the course of their disease, and therefore a careful assessment of risk and benefit for each patient is warranted in choosing the most appropriate therapy.

Sunitinib is distinguished by the highest objective response rate. For most patients, control of overall disease burden over the long term is more important than objective response. Nevertheless, a subset of RCC patients have bulky, symptomatic disease, and these patients may require a greater degree of tumor burden reduction in the short term. In this context, sunitinib is the most appropriate choice.

Temsirolimus is the only agent to date to demonstrate an overall survival benefit, albeit restricted to a poor-risk subset of patients. The utility of this agent in an unselected, better-risk population awaits further study.

Bevacizumab-based therapy is noteworthy for a favorable toxicity profile. However, this agent requires infusion therapy and subcutaneous injections if interferon is added.

Sorafenib has not yet demonstrated effects in the front-line setting that are as robust as those of the other agents. Still, its oral availability and favorable toxicity profile may make it a reasonable initial choice in a subset of patients.

As noted below, investigation into sequential therapy may help identify which agent is preferred initially, as exposure of RCC tumors to certain agents may affect tumor biology and response to subsequent therapy. We are also missing tools with which to predict benefit in individual patients from individual drugs. While characteristics such as normal hemoglobin may predict for better response to a single agent (eg, to sunitinib), such general clinical features may not distinguish among the multiple available agents. Translational investigation to identify the molecular phenotype of response and resistance to each of the agents is needed.

Ongoing Clinical Investigations in Metastatic RCC

Other Targeted Agents

- **Everolimus**—An orally bioavailable derivative of the immunosuppressant macrolide rapamycin that targets mTOR kinase, everolimus (RAD-001, Certican) has shown activity in preclinical models of the cancer. In a phase II study, the clinical efficacy of everolimus in patients with metastatic RCC was evaluated.[35] A total of 25 patients with progressive metastatic RCC were treated with everolimus at a dose of 10 mg daily with continuous dosing. The primary endpoint of the study was time to progression and the secondary endpoint included response rate and toxicity. The median time to progression was 6+ months. A total of 7 patients had partial responses and 11 had stable disease. Treatment-related adverse events included mucositis, skin rash, pneumonitis, hypophosphatemia, hyperglycemia, thrombocytopenia, and anemia. A large phase III trial of RAD-001 vs placebo in treatment-refractory RCC has completed accrual, and results are highly anticipated.

- **Pazopanib**—Pazopanib is an oral multitarget receptor tyrosine kinase inhibitor with potent effects against VEGFR-1, -2, -3, PDGF receptor (PDGFR)-alpha, -beta, and c-kit. A randomized discontinuation trial of pazopanib at 800 mg daily in treatment-refractory RCC patients was preliminarily reported and demonstrated an objective partial response rate of 40%. [36] Toxicity was generally similar to that observed with other small-molecule VEGFR inhibitors, with the notable lower incidence of hand-foot syndrome. A phase III randomized trial of pazopanib vs placebo in cytokine-refractory patients has completed accrual, and results are anticipated.

- **Axitinib**—Axitinib (AG-013736) is a substituted imidazole derivative that inhibits the tyrosine kinase portion of all VEGF receptors and PDGFR-beta at low nanomolar concentrations. A phase II trial of axitinib was conducted in cytokine-refractory RCC patients, demonstrating a 44% objective response rate and a median time to progression of 15.7 months. [37] Treatment-related adverse events included diarrhea, hypertension, fatigue, nausea, and hoarseness. TABLE 2
Select Ongoing/Upcoming Phase II or III Trials in Metastatic RCC

A subsequent trial enrolled sorafenib-refractory RCC patients and demonstrated a partial response in 13 (21%) of 62 evaluable patients, while 55% experienced some degree of tumor regression.[38] One of 14 patients who received both prior sorafenib and prior sunitinib exhibited a partial response. With a median follow-up of 8.1 months, the overall median PFS is 7.4 months. The high objective response rates with this agent and long PFS may be a result of the more potent inhibition of the VEGF receptor. Further study in front-line refractory RCC is planned (Table 2).

• **Perifosine**—Perifosine is a synthetic, substituted heterocyclic alkylphospholipid that has been shown to inhibit Akt activity; it also has cell-dependent effects upon the MAP kinase pathway. Perifosine has demonstrated activity in patients with metastatic RCC in a randomized phase II trial comparing the weekly vs daily dose of perifosine in patients with solid tumors (2 partial responses among 13 RCC patients).[39] In general, perifosine has most commonly been associated with dose-related nausea, vomiting, diarrhea, and fatigue.

Phase I combination trials of perifosine with sunitinib and sorafenib, in addition to a phase II trial in sorafenib/sunitinib-refractory RCC are ongoing. A phase II/III trial of perifosine (with or without sorafenib) vs sorafenib monotherapy is planned.

• **AMG386**—Angiopoietin-1 and -2 (Ang1 and Ang2) are naturally occurring ligands for the Tie2 receptor, which is present on endothelial cells and stimulates angiogenesis upon Ang2 engagement. Selective antagonists of Ang2 have inhibited tumor growth in murine xenograft models.[40] AMG386 is a fusion protein containing a synthetic peptide exhibiting high affinity for angiopoietins fused to the constant region of human IgG1.

AMG386 is administered intravenously weekly and is being studied in combination with several VEGF inhibitors in a phase IB trial. Based on the rationale derived from preclinical data of enhanced antitumor effect in combination with VEGF inhibition, a randomized phase II trial of sorafenib monotherapy vs one of two doses of AMG386 is ongoing in previously untreated metastatic RCC patients (Table 2).

**Treatment Sequences**

The availability and emergence of multiple active monotherapies in RCC has resulted in the clinical use of sequenced therapy. Prior retrospective reviews suggested sequential clinical activity.[41] Despite the lack of prospective data, sequential treatment with VEGF pathway–targeted therapies has become the de facto standard approach in RCC. Thus, prospective investigation of the safety and efficacy of a given targeted agent in the setting of prior exposure to another targeted agent is needed to accurately define the tolerability and clinical benefit of this practice algorithm, as well as studies investigating the mechanisms of progression and resistance to this group of agents.

A study of sunitinib in patients with RECIST-defined disease progression during or within 3 months of bevacizumab-based treatment (N = 61) reported a partial response in 23% of patients, and 75% of patients overall demonstrated some degree of tumor burden reduction.[42] The median PFS was 30 weeks.

Preliminary data have been reported from a phase II trial examining sorafenib in metastatic RCC patients refractory to either sunitinib or bevacizumab.[43] No objective responses were seen, although nine patients (33%)—six who had received prior sunitinib and three, prior bevacizumab—had ≥ 5% decrease in tumor burden ranging from −7% to −20%. The investigators found no association between tumor shrinkage and response to prior therapy. The median PFS was...
3.7 months, with no difference based on prior therapy. Overall, toxicity included hand-foot syndrome, rash, hypertension, diarrhea, and fatigue. There was no difference in toxicity based on prior therapy nor correlation of sorafenib toxicity with toxicity from prior bevacizumab/sunitinib. The only other prospective trial to date is axitinib in sorafenib-refractory RCC noted above. These preliminary data support the concept that an antitumor effect of VEGF-targeted therapy in RCC can be preserved despite prior exposure to VEGF-targeted therapy.

Several prospective trials will provide further insight into treatment sequencing (Table 2). A large phase III trial will randomize sunitinib-refractory RCC patients to either temsirolimus or sorafenib. Such a trial will begin to investigate whether changing drug mechanisms/targets after the failure of VEGF receptor–targeted therapy is of benefit. Additionally, a phase III trial will randomize front-line refractory RCC patients to axitinib or sorafenib to determine whether more potent VEGFR inhibition by axitinib translates into improved clinical benefit in this setting. Finally, a multicenter trial will investigate multiple two-drug sequences. Untreated metastatic RCC patients (N = 240) will be randomized to initial sunitinib, bevacizumab, or temsirolimus, with randomization to one of the two drugs not received initially upon first treatment failure. This approach produces six different two-drug sequences and may provide insight into which sequence(s) produce the longest overall duration of disease control. It may also clarify the impact of a given prior treatment on response to subsequent treatment. In the future, it is hoped that this empiric testing of sequences can be supplemented by knowledge of mechanisms of response and resistance from preclinical studies to guide treatment decisions.

**Combination Therapy**

Oncology drug development has been marked by the testing of combination regimens involving active single agents. Historically, no particularly active single agents have been available for RCC, and no combinations of modestly active agents ever demonstrated a benefit over monotherapy. As combinations of targeted agents undergo investigation, it will be critical for these combinations to demonstrate clinical benefit above and beyond those of sequential monotherapy with the same agents, in order to justify the added toxicity and risk. Thus, prospective data in this regard are critical, and some data have recently emerged.

Several groups have recently reported on the combination of sorafenib and IFN-alpha. A phase II study examined 40 patients with metastatic RCC receiving a standard dose and schedule of IFN-alpha in addition to sorafenib at 400 mg twice daily.[44] This study reported a 33% response rate and a median PFS of 10 months. At the same time, a Southwest Oncology Group (SWOG) trial was reported,[45] with a 19% response rate and 7-month PFS. These trials generate interesting hypotheses about the potential for combinations of cytokine immunomodulatory therapy with antiangiogenic agents. At this point, however, such combinations cannot be recommended for routine use outside of a clinical trial setting. Additional preclinical data have described potentially favorable immunomodulation with sunitinib therapy.[46] Such data may provide a rationale for combination strategies with immunotherapy to optimize antitumor effect. A greater understanding of the pleiotropic effects of targeted agents is needed to rationally build combinations. Combinations of VEGF-targeting agents have also undergone initial testing. The combination of sorafenib and bevacizumab showed preliminary evidence of antitumor activity, but the full doses of each agents were not reached due to dose-limiting toxicity related primarily to hand-foot syndrome, functional stomatitis, anorexia, and fatigue.[47] Sunitinib and bevacizumab have also been combined in two separate phase I trials: one limited to RCC patients and the other enrolling all solid tumors.[48,49] Although a maximum tolerated dose (as defined by dose-limiting toxicities occurring during the first cycle) was not reached in either study, relevant toxicity has occurred with prolonged treatment. Thus, the optimal dose and schedule to optimize efficacy while minimizing toxicity is not yet well-defined. **REFERENCE GUIDE**
Targeting multiple pathways simultaneously may be the optimal combination approach. One such strategy has combined VEGF pathway inhibition with bevacizumab and mTOR pathway inhibition with temsirolimus. A small phase I study (N = 12) reported safety for the active monotherapy doses...
for each drug and preliminary efficacy in the form of tumor burden shrinkage for most patients.[50] This approach is now undergoing phase II testing in treatment-refractory patients and will be compared to bevacizumab plus interferon in a phase III trial (Table 2). Temsirolimus and sorafenib have also been combined in a phase I trial, but full doses were not reached due to toxicity. On a cautionary note about indiscriminate combination of drugs off trial, the combination of sunitinib and temsirolimus was not tolerable, even at the lowest doses of each drug (Temsirolimus, package insert).

An ongoing trial will simultaneously test multiple combinations against bevacizumab monotherapy. The Bevacizumab/Sorafenib/Temsirolimus (BeST) trial, sponsored by the ECOG, will randomize 240 untreated RCC patients to bevacizumab monotherapy or combination therapy with either bevacizumab/sorafenib, bevacizumab/temsirolimus or temsirolimus/sorafenib. This trial will benchmark the PFS of combination therapy against a monotherapy to identify a signal of activity for further testing of one or more combinations.

- **Clinical Trial Considerations**—The emergence of active agents in RCC has far outpaced the ability to rapidly and definitively test all possible permutations of combinations, sequences, and other approaches to maximizing their benefit. Thus, in light of the relatively limited number of RCC patients eligible for clinical trials, several strategies have emerged. The optimal strategy for clinical investigation is not clear. Progression-free survival may be the most practical endpoint, given the probable contamination by subsequent active agents limiting the ability to demonstrate improved overall survival in any one trial. The pending survival analyses in the sunitinib and bevacizumab trials will provide additional data on this issue. Several randomized phase II trials are in progress to estimate the benefit of combinations over monotherapy. While suffering from a lack of power to detect small but meaningful differences, these trials can be useful in selecting the best potential combination, which must then be verified in a larger randomized setting. Given the number of important questions to be addressed, continued support of clinical and translational investigation by cooperative groups, the National Cancer Institute, and Industry is needed.

**Conclusions**

Metastatic RCC is a model solid tumor, in which the elucidation of underlying biology has identified relevant targets. Drugs targeting these pathways have produced robust clinical effects, far surpassing the minimal antitumor activity of historical agents. Further testing of combinations, sequences, and novel agents has the potential to build upon these important advances. Also critical, we will need a deeper understanding of the biology of response and resistance to targeted therapy in order to optimize the use of these agents. Excitement over targeted therapy is balanced by the lack of complete responses, need for chronic therapy, and toxicity of these agents. If the benefit of these drugs could be considered the excitement of a baseball triple, the home run of a cure may be as hard to achieve as stealing home.

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