

Renal Cell Cancer™

U P D A T E

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

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INTERVIEWS

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Renal Cell Cancer Update

A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

Approximately 40,000 new cases of renal cell cancer (RCC) occur annually, with 13,000 deaths due to the disease. Recently, increased understanding of the biology of RCC and emerging clinical trial results have led to the emergence of new therapeutic options for patients. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances. To bridge the gap between research and patient care, *Renal Cell Cancer Update* utilizes one-on-one interviews and round-table discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME activity assists medical oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

- Describe the biology underlying clear cell RCC, including inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene and the pathway leading to VEGF overexpression.
- Examine current treatment options for advanced renal cell carcinoma, including the safety and efficacy of targeted biologic therapies inhibiting VEGF, PDGF and EGF receptors.
- Evaluate the impact of pathologic grade on the selection of therapies and clinical outcomes in RCC and identify molecular targets believed to have clinical relevance in RCC.
- Develop a therapeutic approach for the sequencing and duration of treatment with targeted biologic therapies for the management of RCC.
- Describe ongoing studies in the adjuvant and metastatic settings in order to counsel appropriately selected patients regarding participation.

PURPOSE OF THIS ISSUE OF *RENAL CELL CANCER UPDATE*

The purpose of Issue 1 of *Renal Cell Cancer Update* is to support these global objectives by offering the perspectives of Drs Rini, Figlin and Atkins on the integration of emerging clinical research data into the management of renal cell cancer.

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UPCOMING EDUCATIONAL EVENTS

NCCN Clinical Practice Guidelines in Oncology Symposium™: Kidney Cancer

May 16, 2007
New York, New York
Website: www.nccn.org

ASCO 2007 Annual Meeting

June 1-5, 2007
Chicago, Illinois
Website: www.asco.org

ECOG Semi-Annual Meeting

June 8-10, 2007
Washington, DC
Website: www.ecog.org

CALGB Semi-Annual Meeting

June 21-24, 2007
Baltimore, Maryland
Website: www.calgb.org

14th European Cancer Conference (ECCO)

September 23-27, 2007
Barcelona, Spain
Website: www.fecs.be

The Clinical Trials Workshop

October 26-28, 2007
Denver, Colorado
Website: www.asco.org



INTERVIEW

Brian I Rini, MD

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Tracks 1-20

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| Track 1 | Development of anti-angiogenic therapeutic agents in renal cell carcinoma (RCC) | Track 11 | Rationale for the effectiveness of anti-angiogenic agents in the microscopic versus macroscopic disease setting |
| Track 2 | Phase III trial of interferon with or without bevacizumab as first-line therapy for RCC | Track 12 | Surgical resection after treatment with an MKI for metastatic disease |
| Track 3 | Efficacy of the multikinase inhibitors (MKIs) sunitinib and sorafenib: Clinical implications of sequencing | Track 13 | Identification of responders versus nonresponders to MKIs |
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| Track 7 | Tolerability and side effects of sunitinib and sorafenib | Track 17 | Downstaging RCC for potentially curative resection |
| Track 8 | Hand-foot syndrome associated with sunitinib and sorafenib | Track 18 | Future clinical research strategies in RCC |
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Select Excerpts from the Interview

Track 1

- ▶ **DR LOVE:** Can you discuss the emerging role of the multikinase inhibitors in renal cell cancer?

► **DR RINI:** With an emerging understanding of the biology, it's clear that the angiogenic pathways are relevant to kidney cancer pathophysiology, and as such, several agents have been developed that target various aspects of that pathway. One class of agents includes small-molecule inhibitors of receptors that are present on blood vessels and endothelial cells — receptors for vascular endothelial growth factor, or VEGF.

Agents that block VEGF, such as sunitinib and sorafenib, were both FDA approved in late 2005 or early 2006, because they demonstrated general shrinkage of tumor burden in the majority of patients and objective responses in a smaller subset of patients, ranging anywhere from 10 to up to 40 percent with sunitinib. Sorafenib delayed time to progression in a randomized controlled trial.

Since these FDA approvals, sunitinib was compared to interferon in a front-line study and revealed a fairly dramatic progression-free survival benefit of 11 versus five months and also maintained the response rate of 30 to 40 percent.

Sunitinib has become a front-line reference standard for renal cell cancer. Sorafenib has had less development as initial therapy, and we're waiting on pending clinical trials for this agent.

Track 2

► **DR LOVE:** What do we know about bevacizumab in the treatment of renal cell carcinoma?

► **DR RINI:** Bevacizumab has demonstrated tumor shrinkage of around 70 percent and a respectable progression-free survival in the front-line setting.

A large Phase III trial of bevacizumab with interferon versus interferon alone (1.1) should be reported at ASCO this year. I believe it will establish bevacizumab as a standard component of front-line therapy for renal cell cancer.

1.1

Interferon- α with or without Bevacizumab as First-Line Treatment for Metastatic Renal Cell Carcinoma

Protocol ID: B017705 (AVOREN)
Accrual: 649 (Closed)

Eligibility

- Treatment-naïve patients ≥ 18 years of age
- Metastatic renal cell cancer (clear cell type)
- Nephrectomy
- No proteinuria

R

Interferon + placebo

Interferon- $\alpha 2a$ and placebo

Interferon + bevacizumab

Interferon- $\alpha 2a$ and bevacizumab
10 mg/kg, q2wk

SOURCES: Genentech press release, December 11, 2006; Thomson Centerwatch, March 2007
(www.roche-trials.com/patient/trials/trial10.html).

The trial randomly assigned patients to either interferon alone, which was the standard treatment at the time, or the combination of bevacizumab and interferon.

The study was placebo controlled — patients received either interferon/placebo or interferon/bevacizumab. It was powered to evaluate both overall survival and progression-free survival.

According to a press release issued about the trial, the interim analysis showed that bevacizumab significantly prolonged progression-free survival. In addition, this early analysis indicated a trend toward an improvement in overall survival.

Track 4

► **DR LOVE:** What side effects have been observed with bevacizumab, specifically in renal cell cancer?

► **DR RINI:** The predominant side effects of bevacizumab have been, as in other diseases but perhaps more prominently in renal cancer, hypertension and proteinuria (Yang 2003). The exact mechanism is not well defined, but these are common side effects that probably occur in 30 or 40 percent of recipients.

These events can be Grade III in five or 10 percent of the patients, depending on the definition. Having said that, bevacizumab is a well-tolerated day-to-day drug.

It's administered as an IV infusion every other week, and we do not see many common side effects. Hypertension is generally well managed with standard antihypertensive approaches. Proteinuria is not terribly significant clinically unless it reaches the nephrotic range, which is not common.

Bevacizumab carries the risk of the rare but serious side effects of bleeding, clotting, gastrointestinal perforation and other cardiac issues. Those events are relatively uncommon, but again, they are in the rare but serious category.

Track 7

► **DR LOVE:** Let's talk about the multityrosine kinase inhibitors (MTKIs). Based on your clinical experience, how would you compare the tolerability of sorafenib and sunitinib?

► **DR RINI:** We have no head-to-head comparison, but I believe sorafenib tends to be a little better tolerated. If you had a group of 100 patients receiving each drug, it is probably true that sorafenib would be a little better tolerated, on average. Its side effects generally peak somewhere around weeks four to six, and then they tend to dissipate.

Sunitinib is dosed differently. It's administered intermittently — four weeks on, two weeks off. So those side effects tend to build up over four weeks, resolve over two weeks and then reappear during the dosing period.

The timing, the schedule and the appearance of side effects are different for each agent.

Track 9

► **DR LOVE:** Can you review the paper you recently published about sunitinib and thyroid function in the *Journal of the National Cancer Institute* (Rini 2007)?

► **DR RINI:** We assessed a large number of our patients with metastatic kidney cancer who received sunitinib on one of a variety of trials. We began performing thyroid function tests routinely at baseline and then every two cycles because of reports of thyroid dysfunction associated with sunitinib treatment in patients with GIST. We found that approximately 85 percent of patients (56 out of 66) had one or more abnormalities related to thyroid function.

A smaller subset — approximately half of those patients — had more than one abnormality or exhibited clinical signs or symptoms consistent with hypothyroidism. Seventeen patients received thyroid replacement, and about half of them showed improvement in symptoms.

1.2

ECOG-E2805: Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE)



Select Eligibility Criteria

- Clear cell or nonclear cell renal carcinoma
- Radical or partial nephrectomy
- Intermediate- or high-risk disease
- No evidence of residual or metastatic disease

Target Accrual: 1,332

Current Accrual: 189 (2/24/2007)

Date Activated: April 24, 2006

Study Contacts

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Keith Flaherty, MD, Protocol Co-Chair
Robert Uzzo, MD, Protocol Co-Chair

Cancer and Leukemia Group B
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Southwest Oncology Group
Christopher Wood, MD, Protocol Chair

NCIC-Clinical Trials Group
Michael Jewett, MD, Protocol Chair

SOURCES: NCI Physician Data Query, April 2007; www.ctsu.org.

If patients stay on sunitinib therapy long enough, there is evidence that they are likely to develop hypothyroidism. It should be monitored, and if patients develop hypothyroidism, it should be treated.

Track 10

► **DR LOVE:** Can you discuss the ECOG-E2805 adjuvant trial evaluating sorafenib and sunitinib?

► **DR RINI:** The large Intergroup trial by ECOG started a few months ago and has accrued a few hundred patients with kidney cancer who have undergone a nephrectomy (ECOG-E2805; [1.2]). These patients do not have metastatic disease, but they are at high risk for cancer recurrence based on size, grade, lymph node involvement and other factors. Eligible patients are randomly assigned to placebo, sunitinib or sorafenib for one year. It's a blinded trial, so all the pills are matched.

The primary endpoint is disease-free survival. The target accrual is approximately 1,300 patients, which should take an additional 3 to 3.5 years for enrollment, and then it'll take some time after that to record recurrences and meet the endpoint. ■

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Ryan CW et al. **Sorafenib plus interferon- α 2b (IFN) as first-line therapy for advanced renal cell carcinoma (RCC): SWOG 0412.** *Proc ASCO* 2006; [Abstract 4525](#).

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Yang JC et al. **A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer.** *N Engl J Med* 2003;349(5):427-34. [Abstract](#)



INTERVIEW

Robert A Figlin, MD

Dr Figlin is Arthur and Rosalie Kaplan Professor of Oncology, Chair of the Division of Medical Oncology and Therapeutics Research and Associate Director of Clinical Research at the City of Hope Comprehensive Cancer Center at the City of Hope National Medical Center and Beckman Research Institute in Duarte, California.

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- Track 2** Genetic abnormalities, angiogenesis and the biology of RCC
- Track 3** Incorporation of molecular signatures into the UCLA and Memorial staging systems
- Track 4** Biologic rationale for the development of novel agents in the treatment of RCC
- Track 5** Role of sunitinib and sorafenib in the treatment of good- and intermediate-risk RCC
- Track 6** The mTOR inhibitor temsirolimus for intermediate- or poor-prognosis RCC
- Track 7** Clinical benefits and side effects of the angiogenesis inhibitors in RCC
- Track 8** Clinical trial data on the anti-VEGF monoclonal antibody bevacizumab in RCC
- Track 9** HIF-driven versus VEGF-driven pathways in poor- versus good-risk RCC and the selection of a treatment approach
- Track 10** SELECT trial: Identification of molecular markers to predict benefit from interleukin-2
- Track 11** Clinical algorithm for the treatment of metastatic RCC
- Track 12** Counseling patients about side effects and toxicities with the multikinase and mTOR inhibitors
- Track 13** Hand-foot syndrome associated with sunitinib and sorafenib
- Track 14** Potential differences in the hand-foot syndrome associated with fluoropyrimidines versus MKIs
- Track 15** Combining targeted agents with “vertical and horizontal inhibition” strategies
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- Track 17** Role of novel targeted agents in the treatment of papillary RCC

Select Excerpts from the Interview

Track 1

► **DR LOVE:** Can you track out the recent evolution of clinical trial data in renal cell cancer?

► **DR FIGLIN:** The paradigm with kidney cancer is evolving. In December

2005, sorafenib was approved for metastatic renal cell cancer. In January 2006, sunitinib was approved for advanced renal cell cancer. A plenary session at ASCO 2006 presented data on temsirolimus (Hudes 2006), another agent that will soon become available.

Let me paint the picture for why these agents have resulted in such spectacular benefit. Clear cell kidney cancer most often has a genetic abnormality associated with the von Hippel-Lindau gene, which activates the hypoxia-inducible factor (HIF), which then activates the vascular endothelial growth factor (VEGF) and angiogenesis pathways.

One could imagine that if we had agents that could inhibit HIF or the angiogenesis pathway, alone or in combination, we would have drugs that may be effective for kidney cancer.

In 2007 and through 2008, we will have at least four drugs that meet that description. We have the VEGF receptor tyrosine kinase inhibitors (TKIs) sorafenib and sunitinib, which inhibit the activation of the VEGF receptor. We have bevacizumab, a VEGF ligand antibody that inhibits before activation of the receptor. We also have temsirolimus, which inhibits HIF and therefore angiogenesis.

► **DR LOVE:** Could you clarify how HIF interacts with VEGF?

► **DR FIGLIN:** Angiogenesis is a downstream effect of HIF — HIF activation activates angiogenesis and angiogenesis activates the receptor, all in a sequence of steps. HIF inhibition results in a downregulation of VEGF and other proangiogenic factors. Therefore, if you inhibit HIF, you also inhibit angiogenesis.

Tracks 5-6

► **DR LOVE:** Can you discuss the two MTKIs, sunitinib and sorafenib?

► **DR FIGLIN:** Sunitinib is a small-molecule oral TKI that, when administered to patients with good- and intermediate-prognosis renal cell cancer, significantly improved progression-free survival compared to standard interferon therapy (Motzer 2007).

This treatment is associated with a more than twofold improvement in progression-free survival. This improvement occurs across all treatment groups, including patients with good and intermediate prognoses.

Sorafenib is also a VEGF receptor TKI. It was approved in December 2005 because of a trial demonstrating that sorafenib, when compared to placebo in previously cytokine-treated patients, conferred a significant progression-free survival difference (Escudier 2007; [2.1]).

► **DR LOVE:** What do we know about temsirolimus?

► **DR FIGLIN:** Temsirolimus is an ester of rapamycin that inhibits HIF and is administered intravenously at 25 milligrams weekly. We hope it will be approved by the FDA soon. Patients tolerate the therapy well.

Randomized trials presented last year at ASCO showed a significant improvement in progression-free and overall survival among patients with intermediate- and poor-prognosis renal cell cancer (Hudes 2006).

This has resulted in a dramatic opportunity for patients that heretofore were sent home for hospice care. Temsirolimus is the first treatment that has been shown to produce a survival benefit in renal cell cancer, which is truly no small feat.

2.1

Overall and Progression-Free Survival Following Sorafenib or Placebo in Advanced Clear Cell RCC

	Sorafenib (n = 451)	Placebo (n = 452)	Hazard ratio (95% CI)	p-value
Overall survival (first analysis)*	NR	14.7 months	0.72 (0.54-0.94)	NS
Overall survival (second analysis)†	19.3 months	15.9 months	0.77 (0.63-0.95)	NS
Progression-free survival	5.5 months	2.8 months	0.44	<0.001

* First analysis, prior to treatment crossover, six months' follow-up, May 2005

† Second analysis, following treatment crossover, November 2005

NR = not reached; NS = not significant

SOURCE: Escudier B et al. *N Engl J Med* 2007;356(2):125-34. [Abstract](#)

 **Track 8**

▶ **DR LOVE:** What do we know about bevacizumab and renal cell cancer?

▶ **DR FIGLIN:** Bevacizumab was the first drug in kidney cancer that demonstrated an improvement in progression-free survival (Yang 2003). Although the time to progression was better, it was unclear exactly how to develop the drug.

A series of trials ensued, the second of which we presented last year at ASCO (Bukowski 2006) that compared bevacizumab and erlotinib to bevacizumab and placebo and showed that approximately 13 to 14 percent of patients had objective responses and another 60 to 65 percent of patients had stable disease with bevacizumab.

However, the addition of erlotinib added no benefit with respect to progression-free survival. It appeared that bevacizumab alone showed substantial activity in untreated patients, with progression-free survival in the eight- to nine-month range.

▶ **DR LOVE:** What about objective response rates to treatment with bevacizumab alone?

▶ **DR FIGLIN:** The objective response rate to bevacizumab alone is approxi-

mately 13 to 14 percent among previously untreated patients and about 10 percent among previously treated patients. It is important for the oncologist not to focus only on the response rate. The overall disease-control rate of about 80 percent is the significant piece of information.

Currently, two trials evaluating bevacizumab in RCC are taking place, one in the United States (CALGB-90206; Rini 2004) and one in Europe (BO17705; [1.1, page 4]). Each of these trials is a comparison of bevacizumab/interferon to interferon alone.

A recent press release indicated that BO17705 was a statistically positive trial, with an improvement in progression-free survival in the bevacizumab-treated group compared to the control group (Genentech BioOncology 2006). We expect to hear the results in an oral presentation at ASCO 2007.

- ▶ **DR LOVE:** What is the side-effect and tolerability profile of the combination?
- ▶ **DR FIGLIN:** We don't have much information yet on the side-effect profile of bevacizumab and interferon in combination because it's never been reported except in Phase I trials.

Bevacizumab, when administered alone, has good tolerability. The major side effects when administered intravenously every two weeks are basically hypertension and proteinuria, which could lead to nephrotic syndrome.

Bevacizumab doesn't produce the lethargy, anorexia, hand-foot syndrome and other immunosuppressive complications associated with TKIs. We need to consider carefully what happens when interferon is added because interferon does involve toxicities when administered three times a week.

Track 9

- ▶ **DR LOVE:** Does the fact that temsirolimus has been tested in the patients at high risk make sense biologically?
- ▶ **DR FIGLIN:** We have a clear suggestion (Atkins 2004) that patients with high-risk kidney cancer have a disease that is more often driven by a pathway called mammalian target of rapamycin (mTOR). Temsirolimus is an mTOR inhibitor that inhibits HIF and may be more appropriate for the patient at intermediate or poor risk.

Patients with good and intermediate prognoses may have a more VEGF-driven pathway, and it may be more appropriate to use targeted agents against that specific pathway.

As we better understand the biology of this cancer, we can begin to tailor the multiple treatments to that biology, as opposed to just administering the drugs to all comers. One of the challenges I have as a translational clinical investigator is to help define for practicing oncologists when to use sunitinib, when to use temsirolimus and when neither agent should be used.

► **DR LOVE:** What are the most common tolerability issues patients have with sunitinib and sorafenib?

► **DR FIGLIN:** The most significant dose-limiting toxicity is hand-foot syndrome. It occurs in approximately 20 to 30 percent of patients.

Even Grade I and Grade II hand-foot syndrome can be troublesome for patients. It can affect their ability to walk normally and to carry out normal activities. We must be aware of this early in the course of treatment.

The biology of hand-foot syndrome is not well understood. It's not clear whether it's the inhibition of angiogenesis or "off-target" effects of multitargeted agents, but if you intervene early, hand-foot syndrome is rapidly reversible. ■

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Yang JC et al. **A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer.** *N Engl J Med* 2003;349(5):427-34. [Abstract](#)



INTERVIEW

Michael B Atkins, MD

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Tracks 1-20

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| Track 4 | Development of bevacizumab for RCC | Track 14 | Importance of the initial treatment selection in RCC |
| Track 5 | Efficacy of the mTOR inhibitor temsirolimus in poor-risk RCC | Track 15 | Selection of patients for treatment with interleukin-2 |
| Track 6 | Development of a treatment algorithm for RCC and overcoming resistance to MKIs | Track 16 | Counseling patients to minimize side effects and optimize therapeutic delivery of novel agents in RCC |
| Track 7 | Selection of patients most likely to benefit from interleukin-2 | Track 17 | Temsirolimus-associated side effects and toxicity |
| Track 8 | Combination therapy strategies in RCC | Track 18 | Safety of MKIs in the treatment of CNS metastases |
| Track 9 | Identification of clinical predictors of response to therapeutic agents in RCC | Track 19 | Cytoreductive nephrectomy in patients with RCC |
| Track 10 | Sequencing agents in the treatment of RCC | Track 20 | Challenges in completing adjuvant trials in RCC |

Select Excerpts from the Interview

Track 3

▶ **DR LOVE:** Can you discuss the new biologic agents that are emerging in the treatment of renal cell cancer?

► **DR ATKINS:** Renal cell cancer is unique in that it appears to be the one solid tumor that is directly sensitive to anti-angiogenic or anti-VEGF pathway inhibitors when used as single agents. In other cancers, drugs like bevacizumab have shown activity but all in combination with chemotherapy. That brings into play a lot of other mechanisms.

When we talk about renal cell cancer being sensitive to these agents as single agents, we believe the reason is that kidney cancer cells have “grown up” surrounded by VEGF and haven’t had to work to develop other means of obtaining a blood supply.

This tumor is highly dependent on VEGF, and when you administer a drug like bevacizumab that binds VEGF or a drug that blocks the receptors, like sunitinib or sorafenib, you see almost immediate effects. That’s a unique situation directly related to the biology of kidney cancer.

What are these drugs? One of the two that have been approved in the past year and a half is sorafenib, which is an oral multikinase inhibitor that inhibits Raf within tumor cells and the Raf kinase pathway and the VEGF-R2 receptor within the endothelial cells (Brugarolas 2007; [3.1]).

These two drugs, when administered to patients with advanced renal cell cancer, cause tumor shrinkage in 60 to 80 percent of patients and delay time to progression relative to control therapy.

It’s important to note that a lot of different receptors have tyrosine kinases on them, so these agents are “dirty drugs.” They not only inhibit VEGF-R2, which we believe is responsible for most of their activity, but they also inhibit other kinases. This may contribute to their activity or to their toxicity or may even produce countervailing effects that inhibit their activity.

Track 8

► **DR LOVE:** We’ve seen a lot of interest in combining biologics in different tumor types. Do any combinations make more biologic sense than others in renal cell cancer?

► **DR ATKINS:** Three approaches to combination therapy have been explored in renal cell cancer. One is trying to combine targeted agents — whether targeted against a tumor or the blood vessel — with immunotherapy. Another is combining targeted agents vertically — hitting a particular pathway at two different sites — such as binding the ligand and inhibiting the receptor simultaneously. The third approach is what we call a horizontal blockade, by which you inhibit two different pathways or parallel pathways.

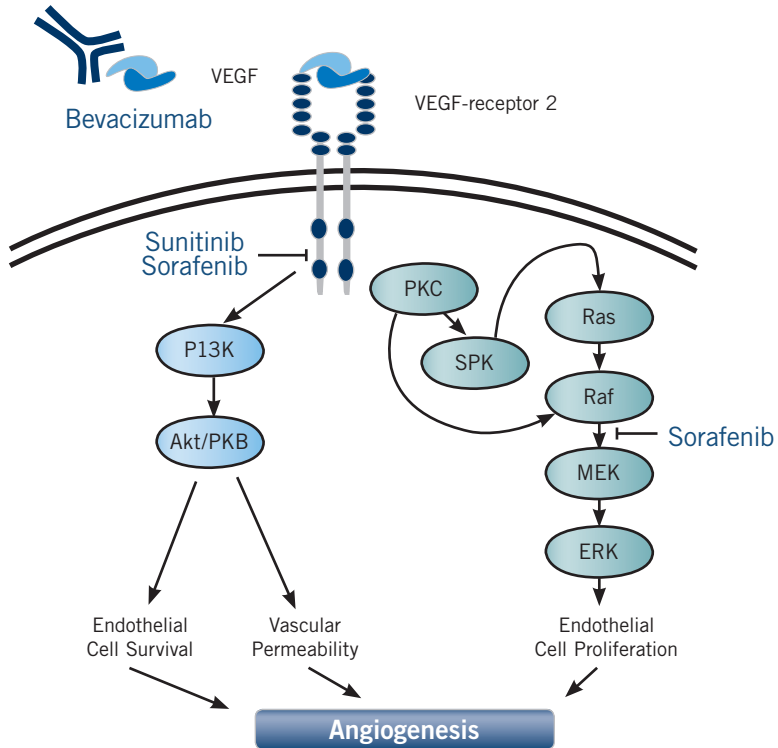
Studies evaluating combinations of targeted agents with immunotherapy include one presented at ASCO last year (Ryan 2006) that evaluated sorafenib in combination with interferon, which will be published shortly. They presented encouraging results, such as 30 percent response rates and no more toxicity than one would expect, and it seems that you can combine those two agents without negative consequences (3.2).

At least in those studies, five or 10 percent of patients showed complete responses, so you might obtain the complete and durable response benefit of immunotherapy with the tumor shrinkage benefits of VEGF receptor therapy.

We will see a similar type of data at ASCO this year on bevacizumab with interferon, which is another approach to combining a targeted agent with immunotherapy, and our group is actively investigating combinations of bevacizumab with high-dose interleukin-2.

3.1

Mechanism of Action of Inhibitors of the VEGF/VEGFR Signaling Pathway



“Bevacizumab binds VEGF, preventing interaction with its receptors and activation of downstream signaling pathway. Sunitinib is an oral tyrosine kinase inhibitor with potent activity against several related protein tyrosine kinase receptors, including VEGFRs 1 to 3. Sorafenib is also an oral multikinase inhibitor that, in addition to inhibiting VEGFRs 1 to 3, also inhibits the serine threonine kinase Raf-1 involved in the Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase (MEK)/extracellular signal-regulated kinase pathway activated after VEGF binding.”

SOURCE: Rini BI. **Vascular endothelial growth factor-targeted therapy in renal cell cancer: Current status and future directions.** *Clin Cancer Res* 2007;13(4):1098-106. With permission from the American Association for Cancer Research. [Abstract](#)

We've spent a lot of time evaluating the vertical inhibition of the VEGF pathway. The theory behind this approach is that when you block the VEGF receptor, you make the cells "hypoxic" and cause increases in circulating VEGF. This could potentially drive angiogenesis if the VEGF receptor isn't completely blocked, so binding the circulating VEGF may create a better block on the pathway.

We found that when you combine sorafenib and bevacizumab, you see more potent activity than with either agent alone. Synergistic activity is seen in close to 50 percent of patients, but the toxicity is also synergistic. We see much more toxicity than with either agent alone and have had to reduce the dose of each agent significantly to find a tolerable dose.

The more promising approach is the horizontal blockade with combination therapy, by which you might inhibit two pathways at the same time.

For example, promising results are being obtained by inhibiting the mTOR pathway and the VEGF pathway together. We're all interested in exploring that further in Phase II trials. Studies have also been launched evaluating sorafenib with temsirolimus.

3.2

SWOG-0412: Grade III or Higher Adverse Events (≥5%) for the Combination of Sorafenib and Interferon-α2b as First-Line Therapy for Advanced Renal Cell Carcinoma

Adverse event	All grades	Grade III+
Fatigue	90%	30%
Diarrhea	62%	11%
Leukopenia	59%	11%
Anorexia	70%	8%
Nausea	64%	5%
Anemia	64%	5%

SOURCE: Ryan CW et al. *Proc ASCO* 2006; [Abstract 4525](#).

 **Track 10**

► **DR LOVE:** What do we know about sequential responses to sorafenib and sunitinib?

► **DR ATKINS:** We know very little. Anecdotal and observational studies are emerging. However, a formal study indicated that sunitinib has activity in patients whose disease progressed after bevacizumab (Rini 2006). You may see tumor shrinkage in close to the same number of patients, although not as robust and for not as long.

It's also beginning to appear that if you take a break and restart the same agent, possibly at a higher dose, you can see a little response again. The physi-

ologic resistance mechanism is plastic in some regards in that if you give a patient a break from that particular agent, you might be able to obtain a benefit again.

I believe we'll see activity in sorafenib after sunitinib failures and sunitinib after sorafenib failures. The real question is, is the response more than you would see if you just put them back on the same agent again?

The greatest potential for seeing sequential activity right now lies in studying mTOR inhibitors in tumors that have become refractory to sunitinib or sorafenib, and those studies are ongoing — big, industry-sponsored trials that will evaluate mTOR inhibition versus placebo or addition of an mTOR inhibitor versus switching to an mTOR inhibitor in patients whose disease progresses on a VEGF receptor TKI.

Track 13

► **DR LOVE:** Based on your clinical experience and the research literature, what are the qualitative and quantitative differences in the side effects of sunitinib and sorafenib in the schedules and doses that are being used right now?

► **DR ATKINS:** I believe sunitinib produces more fatigue, more problems with blood count and more problems with diarrhea and has also been shown to produce hypothyroidism. Also, in a small number of patients, it results in cardiac effects, including decreases in ejection fraction.

Sorafenib is more likely to produce rash and hand-foot syndrome and less likely to produce fatigue, although no formal comparison has been made between the two drugs from a toxicity standpoint. The adjuvant trial that involves sorafenib, sunitinib and a placebo will be a good opportunity to observe the differences in toxicity in patients who don't have disease-related symptoms. ■

SELECT PUBLICATIONS

Azad N et al. **Increased efficacy and toxicity with combination anti-VEGF therapy using sorafenib and bevacizumab.** Presentation. ASCO 2006; [Abstract 3004](#).

Brugarolas J. **Renal-cell carcinoma — Molecular pathways and therapies.** *N Engl J Med* 2007;356(2):185-7. [Abstract](#)

Casanovas O et al. **Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors.** *Cancer Cell* 2005;8(4):299-309. [Abstract](#)

Escudier B et al. **Sorafenib in advanced clear cell renal-cell carcinoma.** *N Engl J Med* 2007;356(2):125-34. [Abstract](#)

Motzer RJ et al. **Sunitinib versus interferon alpha in metastatic renal-cell carcinoma.** *N Engl J Med* 2007;356(2):115-24. [Abstract](#)

Rini BI et al. **Efficacy and safety of sunitinib malate (SU11248) in bevacizumab-refractory metastatic renal cell carcinoma (mRCC).** *Proc ASCO* 2006; [Abstract 4522](#).

Ryan CW et al. **Sorafenib plus interferon- α 2b (IFN) as first-line therapy for advanced renal cell carcinoma (RCC): SWOG 0412.** *Proc ASCO* 2006; [Abstract 4525](#).

QUESTIONS (PLEASE CIRCLE ANSWER):

1. Which of the following have FDA approval for the treatment of advanced renal cell carcinoma?
 - a. Sorafenib
 - b. Sunitinib
 - c. Temsirolimus
 - d. Bevacizumab
 - e. All of the above
 - f. Both a and b

2. First-line therapy with sunitinib resulted in a significant improvement in progression-free survival compared to standard interferon therapy among patients with _____.
 - a. Good- to intermediate-risk RCC
 - b. Intermediate- to poor-risk RCC
 - c. Both a and b

3. First-line therapy with temsirolimus resulted in a significant improvement in progression-free survival compared to interferon therapy among patients with _____.
 - a. Good- to intermediate-risk RCC
 - b. Intermediate- to poor-risk RCC
 - c. Both a and b

4. A Phase III trial demonstrated that sorafenib significantly improved progression-free survival compared to placebo among patients who failed prior therapy for RCC.
 - a. True
 - b. False

5. Hand-foot syndrome occurs in _____ of patients treated with sorafenib or sunitinib.
 - a. Two to four percent
 - b. Five to 10 percent
 - c. 20 to 30 percent
 - d. 45 to 60 percent

6. A study of sunitinib and thyroid function revealed that _____ of sunitinib-treated patients developed one or more abnormalities in thyroid function, which may or may not be clinically significant.
 - a. 66 percent
 - b. 56 percent
 - c. 85 percent
 - d. 17 percent

7. Which of the following agents will be evaluated in ECOG adjuvant trial E2805 (ASSURE)?
 - a. Sunitinib
 - b. Sorafenib
 - c. Temsirolimus
 - d. Bevacizumab
 - e. All of the above
 - f. Both a and b
 - g. a, b and c

8. The mechanism of action for both sorafenib and sunitinib is completely through inhibition of the VEGF tyrosine kinase.
 - a. True
 - b. False

9. The most common side effects of bevacizumab observed in the treatment of RCC include _____.
 - a. Hypertension and proteinuria
 - b. Hand-foot syndrome and fever
 - c. Rash and fatigue

10. The CALGB-90206 and B017705 trials are comparing _____.
 - a. Bevacizumab/interferon to interferon alone
 - b. Bevacizumab/interferon to temsirolimus/interferon
 - c. Sorafenib/interferon to sunitinib/interferon

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To what extent does this issue of *RCCU* address the following global learning objectives?

- Describe the biology underlying clear cell RCC, including inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene and the pathway leading to VEGF overexpression. 5 4 3 2 1 N/A
- Examine current treatment options for advanced renal cell carcinoma, including the safety and efficacy of targeted biologic therapies inhibiting VEGF, PDGF and EGF receptors. 5 4 3 2 1 N/A
- Evaluate the impact of pathologic grade on the selection of therapies and clinical outcome in RCC, and identify molecular targets believed to have clinical relevance in RCC. 5 4 3 2 1 N/A
- Develop a therapeutic approach for the sequencing and duration of treatment with targeted biologic therapies for the management of RCC. 5 4 3 2 1 N/A
- Describe ongoing studies in the adjuvant and metastatic settings in order to counsel appropriately selected patients regarding participation. 5 4 3 2 1 N/A

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Faculty	Knowledge of subject matter	Effectiveness as an educator
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Robert A Figlin, MD	5 4 3 2 1	5 4 3 2 1
Michael B Atkins, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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- Will influence how I practice. 5 4 3 2 1 N/A
- Will help me improve patient care. 5 4 3 2 1 N/A
- Stimulated my intellectual curiosity. 5 4 3 2 1 N/A
- Overall quality of material. 5 4 3 2 1 N/A
- Overall, the activity met my expectations. 5 4 3 2 1 N/A
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Renal Cell Cancer™

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