RCCU | 2006 VOL 1 | ISSUE 1

# Renal Cell Cancer™

## UPDATE

## Conversations with Oncology Investigators

### Bridging the Gap between Research and Patient Care

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*And case presentations and discussion of patients treated by practicing oncologists*

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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 Vogelzang, Bukowski and Dutcher on the integration of emerging clinical research data into the management of renal cell cancer.

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## UPCOMING EDUCATIONAL EVENTS

American Urological Association Kidney and Bladder Cancer Conference
October 6-8, 2006
Miami, Florida
Event website: **auanet.org/kidneybladder**

Chemotherapy Foundation Symposium
Innovative Cancer Therapy for Tomorrow
November 8-11, 2006
New York, New York
Event website: **mssm.edu/tcf**

Society of Urologic Oncology 7th Annual Meeting
December 1-2, 2006
Bethesda, Maryland
Event website: **societyofurologiconcology.org**

ASCO 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Event website: **asco.org**

EDITOR'S NOTE

Neil Love, MD

# Renal cell fireworks

This launch issue of *Renal Cell Cancer Update* includes interviews with three clinical investigators and a tumor panel discussion in which four community-based medical oncologists present cases from their practices that typify the dilemmas facing docs who deal with this somewhat uncommon and highly frustrating malignancy. These cases, which are summarized below, illuminate the rapidly changing algorithm of clinical care for the disease, and of particular interest is the use and selection of the new multikinase inhibitors (MKIs), sorafenib and sunitinib.

**Case 1:** A 59-year-old man presented to a podiatrist with pain in his right foot, and biopsy revealed a 4.5-cm clear cell carcinoma to the right metatarsal. Subsequent CT scans demonstrated a 6.6-cm mass in the left kidney, with no other evidence of disease. The patient was treated with surgical removal of the primary tumor and the metastasis. After several years with no evidence of disease progression, he was diagnosed first with one and then a second isolated adrenal metastasis, which were surgically extirpated. He has not received systemic therapy.

*This case history would be unusual for most solid tumors, but it is common in renal cell cancer. With the emergence of the MKIs, which are significantly less toxic than prior available systemic agents, one wonders if the progression of cases like this one could be slowed by an anti-angiogenic strategy.*

**Case 2:** A 63-year-old man underwent a nephrectomy for a 4.8- x 4.1-cm moderately differentiated clear cell carcinoma with negative nodes and no capsular invasion. After seven months, the patient developed asymptomatic bilateral lung nodules and a right paratracheal lymph node.

*This patient's rapid recurrence after the initial resection places him in a poor-risk category, raising an important question: Assuming it becomes available in the United States, should the mTOR inhibitor temsirolimus (CCI-779 for the diction challenged) be considered? In this instance, the patient received sorafenib on a clinical trial and had a response lasting 14 months. The patient is currently receiving sunitinib. This case demonstrates two important points:*

1. *Several small case series have clearly documented sequential responses to MKIs.*
2. *This man entered a double-blind trial of sorafenib versus placebo. After a couple of*

*months of treatment, the patient, who was randomly assigned to the sorafenib arm, was very concerned that he was receiving a placebo due to a lack of toxicity. This story would not have been told of interferon or interleukin.*

**Cases 3A and 3B:**

***3A:*** A 61-year-old man with a 2-cm mass in the right kidney underwent a right partial nephrectomy, which revealed a Grade I clear cell carcinoma with negative margins. No other evidence of disease appeared on CT scans. Ten months later, the patient developed a 2- x 1-cm right upper lobe lesion of the lung, which was surgically resected.

***3B:*** A 63-year-old woman presented with voiding difficulties and hematuria. A CT scan revealed a 4-cm mass in the right kidney, and she underwent radical nephrectomy, which demonstrated clear cell histology with some papillary features and no lymphovascular invasion.

*A new Intergroup adjuvant trial will compare sorafenib, sunitinib and placebo, but is there currently a role off protocol for adjuvant therapy or treatment of Stage IV NED with these agents?*

**Case 4:** A 74-year-old man presented with bilateral renal masses on ultrasound. Biopsy revealed clear cell carcinoma, and the patient underwent a laparoscopic cryosurgical ablation of the smaller lesion followed by radical nephrectomy to remove the other tumor. Pathology confirmed a 7-cm clear cell carcinoma confined to the kidney with negative nodes.

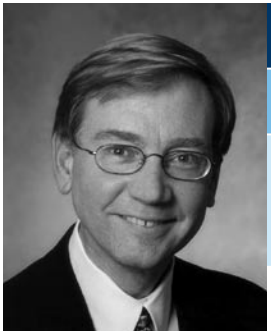
*Nephron-sparing surgery includes many creative options, as demonstrated by this case. However, the challenge of administering antitumor agents to patients with renal and/or hepatic dysfunction is accentuated by the modest available clinical trial data attempting to answer this question.*

**Case 5:** A 63-year-old man presented with a two-month history of malaise, loss of appetite and right upper-quadrant discomfort. CT revealed an enlarged liver with probable metastatic disease and an 8-cm right kidney mass. Liver biopsy revealed a moderately differentiated papillary carcinoma of presumed renal origin.

*Although the clinical research database on clear cell cancer is significant and growing, minimal data are available to guide decision-making for less common tumors such as papillary and collecting duct cancers.*

The encouraging recent results of anti-angiogenic therapies such as the MKIs and bevacizumab seem understandable in view of the long-known "bloody" nature of renal cell cancer. Fortunately, these interventions, along with other targeted approaches such as CCI-779, have the potential to alter the natural history of this disease and to provide clinicians the artillery to more effectively manage cases like those presented on this program.

**— Neil Love, MD**
**NLove@ResearchToPractice.net**
**July 25, 2006**



INTERVIEW

## Nicholas J Vogelzang, MD

Dr Vogelzang is Director of the Nevada Cancer Institute and Professor of Medicine at the University of Nevada School of Medicine in Las Vegas, Nevada.

### Tracks 1-18



## Select Excerpts from the Interview

### Tracks 3-4

**DR LOVE:** What's the pathogenesis when you have an abnormality in the von Hippel-Lindau (VHL) gene?

**DR VOGELZANG:** It turns out that the VHL gene product is an ubiquitination enzyme. A protein called an ubiquitin protein marks cellular proteins for destruction. You put a string of ubiquitins on a protein, and it's basically flushed down the toilet — the toilet being the proteosome. The VHL protein is an ubiquitination ligase. It ties an ubiquitin protein to other proteins.

Primarily, it ubiquitinates hypoxia-inducible factor, or HIF. HIF protein levels increase under hypoxic conditions.

What does HIF do? It is an important protein and gene — it controls nearly 200 proteins, which regulate activities such as glucose transport, erythropoietin production and VEGF production (1.1).

In a hypoxic environment, erythropoietin and hemoglobin are increased and more glucose transport is produced. Likewise, under the conditions of an abnormal VHL, HIF is not eliminated. It sticks around, and instead of being flushed down the toilet, HIF protein increases; it's not targeted for destruction. HIF becomes more active and produces these 200 or so proteins that it controls; one of them happens to be VEGF.

We now know that of the clear cell tumors — 70 to 80 percent of all kidney cancers are clear cell — a majority are VHL mutated. Therefore, it is probable that all these new agents — sunitinib, sorafenib and anti-VEGF drugs — only are working on those kidney cells that produce HIF and HIF-driven proteins. The nonclear cell tumors and perhaps some of the clear cell tumors are not producing the HIF-driven proteins.

We could group clear cell tumors into two categories: VHL mutated and VHL nonmutated. However, we don't have an easy way to quickly measure that in the blood or in the protein. The hypothesis is that the very well-differentiated renal cells will be responsive to these agents and the very poorly differentiated, aggressive tumors will not (Teh 2006).

## Track 5

**DR LOVE:** Can you talk more about the VEGF pathways and the various biologic agents within renal tumors?

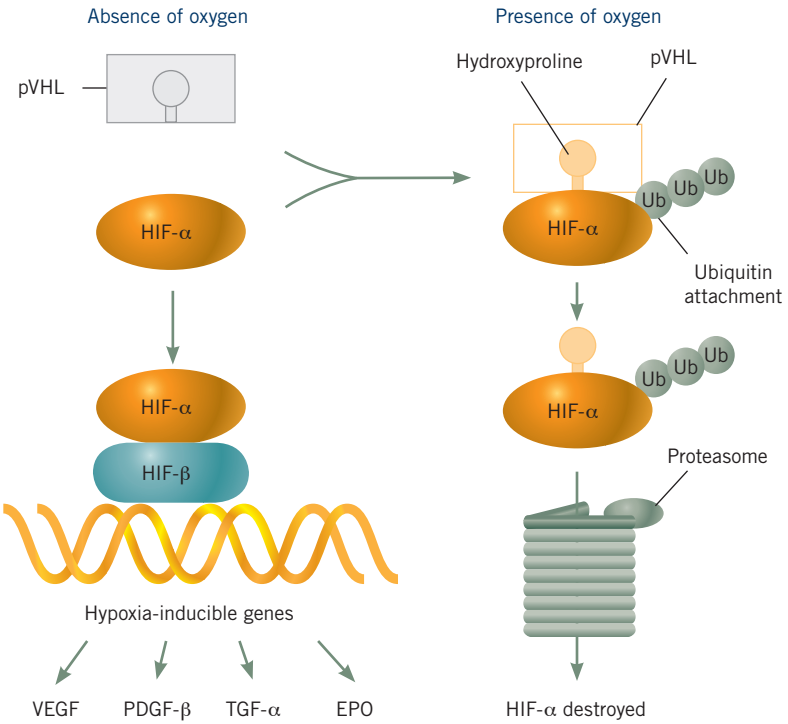
**DR VOGELZANG:** Let's go back to the story of the von Hippel-Lindau mutation followed by HIF overexpression and overexpression of some 200 proteins. Why did VEGF inhibitors work? VEGF is one of the major factors that is upregulated by HIF, but EGF, PDGF and glucose transporters are also upregulated, and all of these factors provide targets.

Jim Yang was on the team with Bill Kaelin, who developed the HIF story (Hoffman 2001; George 2003), and he evaluated a VEGF inhibitor in a placebo-controlled trial (Yang 2003). Results from his study indicated that low-dose and high-dose bevacizumab definitely slowed the cancer down. Not many PRs were present, but the cancer slowed down.

This was a critical finding because it linked the molecular biology of renal cell cancer to clinical treatment. We have known for decades that renal cell carcinoma is hypervascular.

**1.1**

## Control of HIF by the Gene Product of the VHL Gene (pVHL) in the Presence or Absence of Oxygen




HIF is a heterodimer consisting of an α subunit and a β subunit. In the presence of oxygen, HIF-α is hydroxylated on one of two proline residues. The pVHL binds to hydroxylated HIF-α and directs the attachment of a polyubiquitin chain, which targets HIF-α for destruction by a multiprotein complex called the proteasome. Under hypoxic conditions, or in the absence of pVHL, HIF-α accumulates and activates the transcription of hypoxia-inducible genes. VEGF denotes vascular endothelial growth factor, PDGF-β platelet-derived growth factor β, TGF-α transforming growth factor α, and EPO erythropoietin.



## Track 6

**DR LOVE:** Can you discuss the reason that clear cell carcinoma does not respond well to chemotherapy, particularly compared to other common tumors, such as breast, lung and colorectal cancer?

**DR VOGELZANG:** Clear cell carcinoma arises from the proximal tubule, which is bathed in "awful" acidic urine. I conceptualize it as a leathery, thick skin cell because it has to survive in an acidic, toxic environment. It's a tough cell.

These cells also overexpress P-glycoprotein, which is the transport protein that helps get proteins from the urine back into the tissues. The kidney and kidney cancer cells vastly overexpress P-glycoprotein, which is probably why drugs like paclitaxel, doxorubicin and the epothilones don't work and, it is my belief, why the antimetabolites work. Gemcitabine and capecitabine work, but not very well.

Renal cell carcinoma does not respond to chemotherapy, and therefore everybody pursued other agents, such as the cytokines, nontraditional chemotherapies and lately anti-VEGF agents.

## Track 10

**DR LOVE:** Let's talk about the biggest debate that will come out of ASCO 2006: What are the current first- and second-line therapies for patients with average-risk renal cell tumors?

**DR VOGELZANG:** Better-risk patients — like those who have had their kidney removed; whose hemoglobin, calcium and LDH are normal; people who only have one site of disease or are feeling good — have a very good survival rate, and you could treat them with a relatively nontoxic agent. I believe sunitinib and sorafenib are equally good, although they have not been compared yet and they never are likely to be compared in the metastatic setting.

Sorafenib has been shown to extend life in the second line; sunitinib has now beaten interferon in progression-free survival as first-line therapy but has not yet been reported as an overall survival advantage, although we all believe it will be.

I would argue that it doesn't matter which agent you administer first. ■

## SELECT PUBLICATIONS


Atkins MB et al. **Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma.** *J Clin Oncol* 2004;22:909-18. **Abstract**

Beckwith JB, Palmer NF. **Histopathology and prognosis of Wilms tumors: Results from the First National Wilms' Tumor Study.** *Cancer* 1978;41:1937-48. **Abstract**

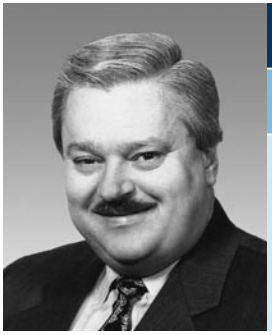
Carroll PR et al. **Abnormalities at chromosome region 3p12-14 characterize clear cell renal carcinoma.** *Cancer Genet Cytogenet* 1987;26:253-9. **Abstract**

George DJ, Kaelin WG Jr. **The von Hippel-Lindau protein, vascular endothelial growth factor, and kidney cancer.** *N Engl J Med* 2003;349:419-21. No abstract available

Hoffman MA et al. **Von Hippel-Lindau protein mutants linked to type 2C VHL disease preserve the ability to downregulate HIF.** *Hum Mol Genet* 2001;10:1019-27. **Abstract**

Hudes G et al. **A phase 3, randomized, 3-arm study of temsirolimus (TEMSR) or interferon-alpha (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor-risk patients with advanced renal cell carcinoma (adv RCC).** *Proc ASCO* 2006;**Abstract LBA4**.

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



INTERVIEW

## Ronald M Bukowski, MD

Dr Bukowski is Director of Experimental Therapeutics at the Cleveland Clinic Foundation Taussig Cancer Center and Professor of Medicine at CCF Lerner College of Medicine of Case Western Reserve University in Cleveland, Ohio.

### Tracks 1-15



## Select Excerpts from the Interview

### Track 6

**DR LOVE:** What do you speculate would be seen in a head-to-head trial comparing sorafenib and sunitinib as first-line therapy?

**DR BUKOWSKI:** I believe the two drugs would come out pretty close. One of the issues revolves around the side-effect profiles and which drug is easier to tolerate, and the other issue is which drug is more powerful in terms of its effect on the surrogates of clinical benefit.

The surrogates are delaying progression of the cancer or improving survival, because response — although it's important — is not the endpoint we focus on, unless patients are symptomatic, which is not the case for the vast majority.

When you look at the two drugs, you see that the major response rates

by RECIST (Response Evaluation Criteria in Solid Tumors) are different — higher with sunitinib than with sorafenib (Motzer 2006b; Escudier 2005). The numbers of patients who actually have a decrease in their tumor size are similar at about 70 to 75 percent. Overall, the same number of patients benefit. The magnitude may be slightly different in terms of response, but response doesn't necessarily control the progression times or survival.

### Track 7

**DR LOVE:** What do we know about sequencing sorafenib and sunitinib in terms of the response to one after treatment with the other?

**DR BUKOWSKI:** We have few data for sequencing, but that's probably the way these agents will be used. Our group presented data on a series of patients who received treatment with one multikinase inhibitor (MKI), such as sunitinib or sorafenib, and then were placed on the other after their disease progressed. We found a series of patients who clearly responded to the second MKI (Tamaskar 2006).

When doctors in the community begin to treat patients with these drugs, they have to understand that no specific duration of treatment is recommended. Ordinarily, we use disease progression as the indicator to stop a drug or start a new drug. Here, although disease progression is looked for, we don't necessarily use that as an indicator to stop or to change treatment.

We have continued — in many of the clinical trials that have been presented — with the same MKI in the face of progressive disease should the patient not have new or worse symptoms. The assumption is that continued inhibition of the VEGF pathway is the important part, and if you take away that inhibition quickly without providing another way to inhibit that pathway, whether it's bevacizumab or another kinase inhibitor, you could have deleterious effects.

### Tracks 9, 11

**DR LOVE:** Can you compare the side effects and toxicities associated with sunitinib and sorafenib?

**DR BUKOWSKI:** They are different, and the differences probably relate to the kinases they inhibit. Kinases are ubiquitous to all cells in the body. Hence, you might expect some of these drugs to have unsuspected toxicities. With sunitinib, the predominant toxicity is fatigue. Interferon has the same, if not greater, toxicity in terms of fatigue (Motzer 2006a; [2.1]), but the fatigue is sometimes limiting in terms of the dose.

If you use 50 mg/day of sunitinib continuously, fatigue becomes overriding. Patients can't tolerate that dose continuously. The longer they receive the drug, the longer it takes for them to recover. Sometimes patients need up to three weeks to make a full recovery from the fatigue. The alternative is to lower the dose to 37.5 mg/day, which is the second dose level for sunitinib.

**2.1**

### Phase III Randomized Trial of Sunitinib versus Interferon-α (IFN-α) as First-Line Systemic Treatment of Metastatic Renal Cell Carcinoma

| Treatment-related adverse events | Sunitinib (%) | | IFN-α (%) | |
|---|---|---|---|---|
| Event | All Grade | Grade III/IV | All Grade | Grade III/IV |
| Fatigue | 51 | 7 | 51 | 11/<1* |
| Diarrhea | 53 | 5* | 13 | 0 |
| Nausea | 44 | 3 | 33 | 1 |
| Stomatitis | 25 | 1 | 2 | <1 |
| Hypertension | 24 | 8* | 1 | <1 |
| Hand-foot syndrome | 20 | 5* | 1 | 0 |
| Ejection fraction decline | 10 | 2 | 3 | 1 |
| Pyrexia | 7 | 1 | 34 | 0 |
| Chills | 6 | 1 | 29 | 0 |
| Myalgia | 5 | <1 | 16 | <1 |
| Flu-like symptoms | 1 | 0 | 8 | <1 |

* Greater frequency, $p < 0.05$

SOURCE: Motzer RJ et al. *Proc ASCO* 2006a;**Abstract LBA3**.

**DR BUKOWSKI:** Sorafenib is an easier drug to use than sunitinib; it has fewer side effects. Its two main side effects are skin toxicity and diarrhea, occurring in about 30 percent of patients (Escudier 2005). The diarrhea is not a problem; you can control it with diphenoxylate/atropine or loperamide.

The skin toxicity is generally what has required dose reductions. It's hand-foot syndrome, as with the fluoropyrimidines. These patients develop some redness and tenderness. I believe dose modifications because of hand-foot syndrome are required in one third or more of patients.

In the study presentation by Dr Escudier at ASCO 2006, in which he presented the toxicity data for previously untreated patients, about 50 percent experienced hand-foot symptoms of any grade (Escudier 2006; [2.2]).

## Track 13

**DR LOVE:** Can you discuss CCI-779, or temsirolimus?

**DR BUKOWSKI:** Temsirolimus is an interesting drug with a different target. It inhibits a kinase called mammalian target of rapamycin (mTOR). The study presented at ASCO 2006 was a Phase III trial for patients with renal cell cancer. The investigators didn't select for patients with clear cell carcinoma, but they did select patients who would be expected to have poor-prognosis metastatic disease. The expected survival of the group was four to five months.

**2.2**

**Phase II Randomized Trial of Sorafenib versus Interferon in Treatment-Naïve Patients with Advanced Renal Cell Carcinoma: Incidence of Select Drug-Related Adverse Events ≥ 2%**

| | Sorafenib (n = 97) | | Interferon (n = 92) | |
|---|---|---|---|---|
| | Any Grade | Grades III/IV | Any Grade | Grades III/IV |
| Cardiac general | 28 (29%) | 4 (4%) | 7 (8%) | 0 (0%) |
| Hypertension | 25 (26%) | 3 (2%) | 4 (4%) | 0 (0%) |
| Constitutional symptoms | 50 (52%) | 5 (5%) | 62 (67%) | 12 (13%) |
| Fatigue | 43 (44%) | 3 (3%) | 45 (49%) | 9 (10%) |
| Gastrointestinal | 75 (77%) | 9 (9%) | 53 (58%) | 8 (9%) |
| Diarrhea | 49 (51%) | 4 (4%) | 10 (11%) | 0 (0%) |
| Nausea | 21 (22%) | 1 (1%) | 31 (34%) | 4 (4%) |
| Dermatology/skin | 71 (73%) | 15 (16%) | 20 (22%) | 0 (0%) |
| Rash | 39 (40%) | 5 (5%) | 3 (3%) | 0 (0%) |
| Hand-foot skin reaction | 50 (52%) | 10 (10%) | 3 (3%) | 0 (0%) |

SOURCE: Escudier B et al. *Proc ASCO* 2006;**Abstract 4501**.

Is there any reason to suggest that sunitinib or sorafenib cannot be administered to this type of patient? No. I believe you can use those agents for these patients, and you'll probably have the same effects.

Temsirolimus, however, has been tested only in that group of patients. It did produce an improvement in survival compared to interferon (Hudes 2006). The group receiving temsirolimus at 25 mg once a week had a median survival of about 10.9 months. It was a three-month advantage in median survival, but it was significant. It's a drug that clearly has an effect. We have to learn how to use it and determine its place in the treatment of this disease.

## Track 14

**DR LOVE:** Assuming temsirolimus were available, how would you put sorafenib, sunitinib and temsirolimus together in your clinical treatment algorithm?

**DR BUKOWSKI:** For the untreated patient with clear cell carcinoma, you have two choices: sunitinib or sorafenib. Probably, given the data presented (Motzer 2006a; [2.3]), sunitinib will be used. It was the featured drug at the ASCO 2006 Plenary Session. I have no doubt that will influence the vast majority of medical oncologists because the data are pretty solid with the drug.

When those patients progress — and all of them do — you should consider the second kinase inhibitor, sorafenib, as a drug to follow up in the sequential therapy for this disease. If you're convinced that a subset of patients respond badly and have rapidly progressive disease, temsirolimus is a drug you can use in that situation.

**DR LOVE:** Are there any patients in whom you'd initiate sorafenib rather than sunitinib?

**DR BUKOWSKI:** There are patients in whom you can use sorafenib initially — those who have minimal symptoms and in whom you want to avoid the side effects associated with sunitinib.

I believe the medical oncology community will start to use both of these drugs, and they will decide for themselves which of the two is the most favorable in terms of side effects. They probably have fairly similar effects on the biology of the disease.

**2.3**

**Phase III Randomized Trial of Sunitinib versus Interferon-α (IFN-α) as First-Line Systemic Treatment of Metastatic Renal Cell Carcinoma**

| Response* | Sunitinib (n = 335) | IFN-α (n = 327) | *p*-value |
|---|---|---|---|
| Objective response | 31% | 6% | <0.000001 |
| Partial response | 31% | 6% | — |
| Stable disease | 48% | 49% | — |
| Progression of disease/ not evaluable | 21% | 45% | — |
| **Survival*** | **Sunitinib** | **IFN-α** | |
| Median PFS† (95% CI) | 11 mo (10-12 mo) | 5 mo (4-6 mo) | <0.000001† |

* By independent central review; † HR = 0.415; (95% CI: 0.320-0.539)

SOURCE: Motzer RJ et al. *Proc ASCO* 2006a;**Abstract LBA3**.

## Track 15

**DR LOVE:** What are the key ongoing clinical trials for renal cell cancer in the adjuvant setting?

**DR BUKOWSKI:** One important study in the United States will compare sunitinib, sorafenib and placebo (ECOG-E2805; [2.4]) as adjuvant therapy. The investigators plan to administer these agents for a year. I believe that it will be difficult to treat the vast majority of patients for one year with sunitinib; it may be a little easier with sorafenib.

**DR LOVE:** What do you think will be the key issues with each of these drugs in administering them for a year?

**DR BUKOWSKI:** With sunitinib, I believe it will be fatigue. I don't know that patients will tolerate this drug because of the fatigue, and it will require dose reductions. With sorafenib, it will be skin toxicity. Remember, sorafenib is administered continuously. These drugs should be administered continuously because they don't cure the disease; they suppress it.

Sunitinib is administered on a four-week-on, two-week-off schedule, which is less than optimal. The two-week-off period was developed to let patients recover from the toxicities. During those two weeks, however, some patients' symptoms start to recur, and the disease may start to progress. ■

**2.4**

### Phase III Randomized Study of Adjuvant Sunitinib Malate versus Sorafenib in Patients with Resected Renal Cell Carcinoma

Protocol IDs: ECOG-E2805, CALGB-E2805, CANNCIC-E2805, SWOG-E2805, NCT00326898, CTSU
Target Accrual: 1,332 (Open)

**Eligibility**
Clear cell carcinoma, nonclear cell carcinoma (excluding collecting duct or medullary), intermediate- or high-risk disease

R

- Oral sunitinib qd days 1-28 + oral placebo for sorafenib BID days 1-42
- Oral sorafenib BID days 1-42 + oral placebo for sunitinib qd days 1-28
- Oral placebo for sorafenib BID days 1-42 + oral placebo for sunitinib qd days 1-28

In all arms, treatment repeats every six weeks for up to nine courses in the absence of disease progression or unacceptable toxicity.

Trial Lead Organizations:

Eastern Cooperative Oncology Group
Naomi Balzer-Haas, MD, Protocol Chair
Tel: 888-369-2427

Southwest Oncology Group
Christopher Wood, MD, Protocol Chair
Tel: 800-392-1611

SOURCE: NCI Physician Data Query, July 2006.

## SELECT PUBLICATIONS


Escudier B et al. **Randomized phase II trial of the multi-kinase inhibitor sorafenib versus interferon (IFN) in treatment-naïve patients with metastatic renal cell carcinoma (mRCC).** *Proc ASCO* 2006;**Abstract 4501**.

Escudier B et al. **Randomized Phase III trial of the Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC).** *Proc ASCO* 2005;**Abstract 4510**.

Hudes G et al. **A phase 3, randomized, 3-arm study of temsirolimus (TEMSR) or interferon-alpha (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor-risk patients with advanced renal cell carcinoma (adv RCC).** Presentation. *Proc ASCO* 2006;**Abstract LBA4**.

Motzer RJ et al. **Phase III randomized trial of sunitinib malate (SU11248) versus interferon-alfa (IFN-α) as first-line systemic therapy for patients with metastatic renal cell carcinoma (mRCC).** *Proc ASCO* 2006a;**Abstract LBA3**.

Motzer RJ et al. **Sunitinib in patients with metastatic renal cell carcinoma.** *JAMA* 2006b;295(21):2516-24. **Abstract**

Shaheen PE et al. **Thyroid function tests (TFTs) abnormalities in patients (pts) with metastatic renal cell carcinoma (mRCC) treated with sunitinib.** *Proc ASCO* 2006;**Abstract 4605**.

Tamaskar I et al. **Antitumor effects of sorafenib and sunitinib in patients (pts) with metastatic renal cell carcinoma (mRCC) who had prior therapy with anti-angiogenic agents.** *Proc ASCO* 2006;**Abstract 4597**.

INTERVIEW

## Janice P Dutcher, MD

Dr Dutcher is Professor of Medicine at New York Medical College and Associate Director for Clinical Affairs at the Our Lady of Mercy Medical Center Comprehensive Cancer Center in Bronx, New York.

### Tracks 1-11



## Select Excerpts from the Interview

### Track 8

**DR LOVE:** Can you discuss the randomized discontinuation study of sorafenib for patients with metastatic renal cell carcinoma?

**DR DUTCHER:** This study had an interesting design. The concept was that these drugs would not necessarily produce complete or partial responses, but they would delay tumor growth, and therefore we would see delay in progression.

This design is probably more acceptable in renal cell treatment than it is for other tumors. Obviously, survival is the ultimate endpoint, but the surrogate is progression-free survival. If we're not going to see responses, then we want to determine whether the drug will affect the natural history of the disease.

In the randomized discontinuation trial, all the patients received sorafenib for 12 weeks. Then, if they experienced 25 percent shrinkage as measured by RECIST, that was seen as some evidence of response, and they continued on the treatment. If they had 25 percent growth, they were taken off the treatment.

If at 12 weeks they were somewhere in the middle — no growth, no shrinkage — they were randomly assigned to a placebo or to continue sorafenib for another 12 weeks. At the end of 24 weeks, the number of patients on sorafenib who had not progressed compared to the placebo had doubled (Ratain 2006; [3.1]).

The randomized discontinuation trial demonstrated that sorafenib had some effect and continuing it had some effect and that when sorafenib was stopped, growth of the tumor continued. It showed ability to inhibit progression, so that was the basis for the randomized placebo-controlled study known as the TARGETs trial.

**DR LOVE:** What did the TARGETs trial show?

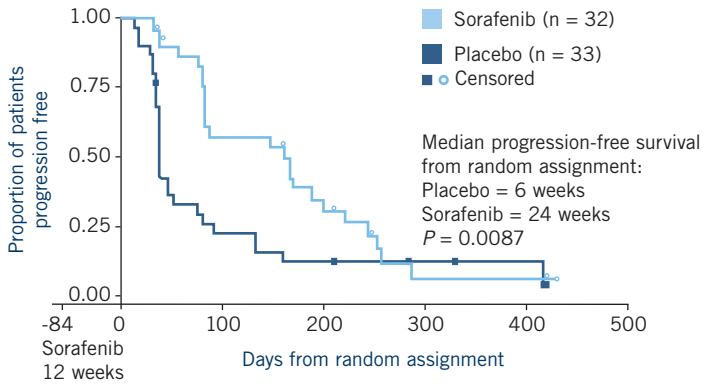
**DR DUTCHER:** This was an international study of sorafenib versus placebo for patients who had received one prior systemic therapy for advanced renal cell carcinoma. There was a significant improvement in progression-free survival for the patients on sorafenib (Escudier 2005; [3.2]).

The difficulty with this study is that once the progression-free survival was observed, it was felt to be unethical to continue the trial with a placebo. The patients were unblinded, and patients receiving the placebo were allowed to receive sorafenib; that may confound the survival data.

Data presented at ASCO in 2006 demonstrated that patients who crossed over received benefit from starting sorafenib, even after having progressed on the placebo (Eisen 2006). It's pretty clear that we will see continued benefit in both arms of that study. ■

**3.1**

**Sorafenib Discontinuation Trial: Median Progression-Free Survival from Randomization**




SOURCE: Ratain MJ et al. **Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma.** *J Clin Oncol* 2006;24(16):2505-12. Reprinted with permission from the American Society of Clinical Oncology. **Abstract**

## 3.2 Phase III TARGETs Trial: Sorafenib versus Placebo

**Initial efficacy data[1]**

| Parameter | Sorafenib (n = 335)* | Placebo (n = 337)* |
|---|---|---|
| Best response (RECIST)† | | |
| Partial response | 2% | 0% |
| Stable disease | 78% | 55% |
| Progressive disease | 9% | 30% |
| Missing | 11% | 15% |
| 12-week progression-free rate | 79% | 50% |

* Patients randomly assigned at least six weeks before data cutoff of January 28, 2005
† Objective responses by independent review

**Summary of crossover analysis[2]**

| Overall survival | Sorafenib | Placebo | Hazard ratio (95% CI) | *p*-value |
|---|---|---|---|---|
| At time of crossover* | Not reached | 14.7 months | 0.72 (0.55, 0.95) | 0.018 |
| At six months postcrossover | 19.3 months | 15.9 months | 0.77 (0.63, 0.95) | 0.015 |
| At six months postcrossover with placebo censored | 19.3 months | 14.3 months | 0.74 (0.58, 0.93) | 0.0094 |

* Censored observation

SOURCES: [1] Escudier B et al. *Proc ASCO* 2005;**Abstract 4510**. [2] Eisen T et al. *Proc ASCO* 2006;**Abstract 4524**.

## SELECT PUBLICATIONS


Dhanda R et al. **A comparison of quality of life and symptoms in kidney cancer patients receiving sorafenib versus placebo.** *Proc ASCO* 2006;**Abstract 4534**.

Eisen T et al. **Randomized phase III trial of sorafenib in advanced renal cell carcinoma (RCC): Impact of crossover on survival.** *Proc ASCO* 2006;**Abstract 4524**.

Escudier B et al. **Randomized Phase III trial of the Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC).** *Proc ASCO* 2005;**Abstract 4510**.

Gollob J et al. **Phase II trial of sorafenib plus interferon-alpha 2b (IFN-α2b) as first- or second-line therapy in patients (pts) with metastatic renal cell cancer (RCC).** *Proc ASCO* 2006;**Abstract 4538**.

Ratain MJ et al. **Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma.** *J Clin Oncol* 2006;24(16):2505-12. **Abstract**

Ryan CW et al. **Sorafenib plus interferon-α2b (IFN) as first-line therapy for advanced renal cell carcinoma (RCC): SWOG 0412.** *Proc ASCO* 2006;**Abstract 4525**.

Teh BT et al. **Gene expression profiling identifies two distinct papillary renal cell carcinoma (RCC) subgroups of contrasting prognosis.** *Proc ASCO* 2006;**Abstract 4503**.

Thomas GV et al. **Hypoxia-inducible factor determines sensitivity to inhibitors of mTOR in kidney cancer.** *Nat Med* 2006;12(1):122-7. **Abstract**

**QUESTIONS (PLEASE CIRCLE ANSWER):**

1. **The von Hippel-Lindau protein is an ubiquitination ligase that ubiquitinates hypoxia-inducible factor (HIF), causing it to be targeted for destruction by the proteasome.**
   a. True
   b. False

2. **A Phase III trial of sunitinib versus interferon-α in the first-line treatment of metastatic renal cell carcinoma revealed that the use of sunitinib was associated with a median PFS of _____.**
   a. Five months
   b. Seven months
   c. 11 months
   d. 18 months

3. **In the Phase III study of first-line therapy, rates of fatigue (all grades) were identical between sunitinib and interferon-α.**
   a. True
   b. False

4. **ECOG-E2805 is a Phase III study comparing _____ for the adjuvant treatment of patients with resected renal cell carcinoma.**
   a. Sunitinib
   b. Sorafenib
   c. Temsirolimus
   d. Placebo
   e. Both a and c
   f. a, b and d

5. **The duration of therapy in the ECOG-E2805 adjuvant trial will be for two years in the absence of disease progression or unacceptable toxicity.**
   a. True
   b. False

6. **Sunitinib is administered on a four-week-on and two-week-off schedule to allow patients to recover from treatment-associated toxicity.**
   a. True
   b. False

7. **Hypothyroidism requiring thyroid replacement occurs in approximately _____ of patients treated with sunitinib.**
   a. 100 percent
   b. 80 percent
   c. 60 percent
   d. 40 percent
   e. 20 percent

8. **CCI-779, or temsirolimus, is an mTOR inhibitor.**
   a. True
   b. False

9. **In a Phase III trial evaluating temsirolimus, interferon or the combination in patients with poor-risk advanced renal cell carcinoma, temsirolimus demonstrated _____.**
   a. A progression-free survival advantage compared to interferon
   b. An overall survival advantage compared to interferon
   c. Both a and b

10. **In the sorafenib randomized discontinuation trial, at the end of 24 weeks a significant improvement in progression-free survival after randomization was achieved with sorafenib — a median of 24 weeks versus six weeks with placebo.**
    a. True
    b. False

11. **In the Phase III TARGETs trial, sorafenib significantly prolonged progression-free survival (24 weeks) compared to placebo (12 weeks) in patients with advanced renal cell carcinoma.**
    a. True
    b. False

12. **In the Phase II trial of sorafenib versus interferon, the incidence of Grade III/IV hand-foot skin reaction and skin rash associated with sorafenib was _____.**
    a. Less than seven percent
    b. 10 percent
    c. 20 percent

*Post-test answer key: 1a, 2c, 3a, 4f, 5b, 6a, 7e, 8a, 9c, 10a, 11a, 12b*

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- 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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|---|---|---|
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| Ronald M Bukowski, MD | 5 4 3 2 1 | 5 4 3 2 1 |
| Janice P Dutcher, MD | 5 4 3 2 1 | 5 4 3 2 1 |

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Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
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.....

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.....

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RCCU106

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