RCCU | 2008 VOL 3 | ISSUE 1

Renal Cell Cancer™ UPDATE

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

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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, an increased understanding of the biology of RCC and emerging clinical trial results have led to new therapeutic options for patients. To bridge the gap between research and patient care, *Renal Cell Cancer Update* utilizes one-on-one interviews with leading oncology investigators. By providing access to expert perspectives on the latest research developments in the context of clinical practice, this CME activity will assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date management strategies for patients with RCC.

LEARNING OBJECTIVES

- Apply an understanding of the biology underlying clear cell RCC, including inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene and the pathway leading to VEGF overexpression, to therapeutic decision-making.
- Construct management strategies for patients with advanced RCC, considering safety and efficacy profiles for 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, assess molecular targets believed to have clinical relevance in RCC and apply this information to clinical practice.
- Develop a therapeutic approach for the sequencing and duration of treatment with targeted biologic therapies for patients with RCC.
- Counsel appropriately selected patients about participation in clinical trials in the adjuvant and metastatic settings.

PURPOSE OF THIS ISSUE OF *RENAL CELL CANCER UPDATE*

The purpose of Issue 1 of *Renal Cell Cancer Update* is to support the learning objectives by offering the perspectives of Drs Motzer, George, Amato and Dutcher on the integration of emerging clinical research data into the management of renal cell cancer.

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This program is supported by educational grants from Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc and Genentech BioOncology.

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CONTENT VALIDATION AND DISCLOSURES

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FACULTY — **Dr Amato** had no real or apparent conflicts of interest to disclose. The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Motzer** — Contracted Research: Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth. **Dr George** — Advisory Committee: Pfizer Inc, Sanofi-Aventis, Wyeth; Consulting Agreements: Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi-Aventis, Wyeth; Paid Research: Amgen Inc, Bristol-Myers Squibb Company, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth; Speakers Bureau: Pfizer Inc, Sanofi-Aventis. **Dr Dutcher** — Advisory Committee: Bayer Pharmaceuticals Corporation, Genentech BioOncology, Onyx Pharmaceuticals Inc, Pfizer Inc, Wyeth; Consulting Agreement: Novartis Pharmaceuticals Corporation; Data Safety and Monitoring Board: Bristol-Myers Squibb Company, Medarex Inc; Paid Research: Bayer Pharmaceuticals Corporation, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth; Speakers Bureau: Bayer Pharmaceuticals Corporation, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Pfizer Inc, Wyeth.

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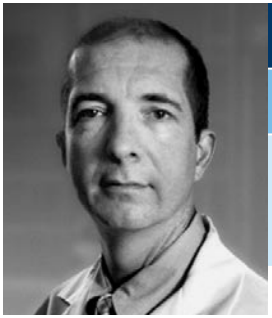

INTERVIEW

Robert J Motzer, MD

Dr Motzer is Attending Physician in the Genitourinary Oncology Section at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-16

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Can you provide an overview of the incidence and treatment of RCC?

DR MOTZER: Renal cell cancer afflicts approximately 50,000 people each year in the US and usually occurs in individuals in their sixties. It's the eighth most common cancer in men, with a man-to-woman ratio of two to one.

The standard curative treatment for RCC for many years has been surgical resection of the primary kidney tumor for localized disease. However, RCC is considered a "silent cancer," and often no symptoms occur that lead to early diagnosis. Many patients present with metastatic disease at initial diagnosis or

relapse with metastases after a nephrectomy. For these individuals, this was for many years considered an especially difficult cancer to treat.

Different chemotherapies were tried, and none provided meaningful clinical benefit. It was considered the model for chemotherapy-resistant cancer.

Until recently, the mainstay of systemic treatment for metastases was immunotherapy with the cytokines — interferon and interleukin-2. Both were recognized in the 1980s as having some level of activity, and until recently they remained the only agents that showed activity in this disease.

In the 1990s, through careful work by laboratory-based physicians, a gene was recognized — the von Hippel-Lindau gene — that's frequently mutated and inactive in RCC (1.1). The downstream effects of the gene are to prevent tumor growth and blood vessel formation.

As anti-angiogenic targeted therapies were developed, RCC was recognized as an important cancer in which to study these agents. These anti-angiogenic treatments are paying off and have now been implemented as the standard treatment for RCC.

The newer targeted therapies were initially studied in patients who had been treated with interferon or interleukin-2 and had progressive disease. Bevacizumab — a neutralizing antibody to vascular endothelial growth factor (VEGF) — was the first agent to be studied in a small, randomized trial with patients whose disease progressed on high-dose interleukin-2 (Yang 2003; [1.2]).

Dr Yang and colleagues from the NCI reported a statistically significant improvement in progression-free survival for the patients treated with bevacizumab at 10 mg/kg every two weeks compared to placebo. This study served as a proof of principle that we were on the right track with targeted anti-angiogenic therapies in mRCC.

1.1

Anti-Angiogenesis in Renal Cell Cancer

"In the absence of functional VHL, there is unhindered accumulation of HIF-α despite normal tissue oxygenation, and consequent overexpression of its downstream transcriptional targets such as vascular endothelial growth factor (VEGF), TGF-α, platelet-derived growth factor (PDGF), glucose transporter GLUT-1 and erythropoietin. Several of these proteins favour the development and sustenance of renal tumours by providing unopposed growth stimuli or angiogenic support...

VHL inactivation by mutation or promoter hypermethylation has subsequently been identified in 60-80% of sporadic clear cell RCC. The evaluation of VEGF (and PDGF) antagonists is a logical consequence of the identification of aberrant expression of these molecules in clear cell RCC. Various approaches to target angiogenesis, using antibodies against VEGF, or receptor kinase inhibitors directed against VEGF and/or PDGF receptors (VEGFR, PDGFR) have been successfully explored over the last few years."

SOURCE: Srinivasan R et al. *BJU International* 2007;99:1296-300. **Abstract**

1.2

Phase II Randomized Trial of Bevacizumab versus Placebo for Patients with mRCC Previously Treated with Interleukin-2

	Bevacizumab 10 mg/kg (n = 39)	Bevacizumab 3 mg/kg (n = 37)	Placebo (n = 40)
Median time to progression	4.8 months[1]	3.0 months[2]	2.5 months
Four-month PFS	64%	39%	20%
Eight-month PFS	30%	14%	5%
Partial response rate	10%	0%	0%

PFS = progression-free survival; [1] $p < 0.001$ versus placebo; [2] $p = 0.041$ versus placebo

"In our study, the aim was to neutralize vascular endothelial growth factor with a humanized monoclonal antibody (bevacizumab) in patients with metastatic clear-cell renal cancer.

...We found that the time to tumor progression was prolonged...in patients given 10 mg of bevacizumab per kilogram every two weeks, as compared with patients in the placebo group."

SOURCE: Yang JC et al. *N Engl J Med* 2003;349(5):427-34. **Abstract**

Tracks 3-5

DR LOVE: Can you discuss the development of TKIs for the treatment of RCC?

DR MOTZER: The next agent studied was sorafenib, a multitargeted TKI, which is believed to affect RCC through inhibition of VEGF receptor and platelet-derived growth factor (PDGF) receptor.

Sorafenib was initially evaluated in a randomized, Phase II discontinuation study (Ratain 2006), which is a trial design utilized to evaluate drugs that are expected to effect disease stabilization or to prolong progression-free survival rather than produce classic tumor responses. Approximately two thirds of the patients experienced some degree of tumor shrinkage. In fact, the study demonstrated a prolongation in progression-free survival for sorafenib compared to placebo (Ratain 2006).

That study led to a large, randomized, Phase III trial (TARGET) in which patients with clear cell histology whose disease progressed on prior therapy (interferon or interleukin) were randomly assigned to sorafenib versus placebo (Escudier 2007).

This was the largest trial conducted worldwide in RCC and included more than 900 patients. The response rate was predictably about 10 percent for sorafenib, but progression-free survival was approximately doubled with sorafenib compared to placebo (1.3). The trial was positive, and the patients on the placebo arm were allowed a crossover to sorafenib.

DR LOVE: How do those data compare to what you observed with sunitinib?

1.3

TARGET: Sorafenib versus Placebo for Previously Untreated Patients with mRCC

	Sorafenib (n = 451)	Placebo (n = 452)	HR	*p*-value
Overall survival				
Before crossover	NR	14.7 months	0.72	0.02*
After crossover	19.3 months	15.9 months	0.77	0.02*
Progression-free survival	(n = 335)	(n = 337)		
Before crossover	5.5 months	2.8 months	0.44	0.001

NR = not yet reached; HR = hazard ratio

* Not significant according to O'Brien-Fleming threshold

SOURCE: Escudier B et al; TARGET Study Group. *N Engl J Med* 2007;356(2):125-34. **Abstract**

DR MOTZER: The first sunitinib study was a single-arm trial conducted at five centers with 63 patients whose disease had progressed on first-line cytokine therapy, with sunitinib administered at the standard dose of 50 milligrams daily oral therapy for four weeks followed by two weeks off.

Approximately 40 percent of the patients achieved a partial response, and the median progression-free survival was 8.7 months, which compared favorably to the two to three months that would be expected with inactive agents as part of the historical control (Motzer 2006a). A larger, single-arm pivotal trial was conducted with response as the primary endpoint in second-line treatment (Motzer 2006b), and a large Phase III trial compared sunitinib to interferon alpha as first-line therapy (Motzer 2007; [1.4]).

DR LOVE: What about temsirolimus and its role in the treatment of RCC?

DR MOTZER: Temsirolimus is a unique anticancer agent. It's an mTOR (mammalian target of rapamycin) inhibitor and is the first drug in this class of agents approved for the treatment of advanced RCC. It was originally studied in RCC as part of a randomized Phase II trial of three different dose

1.4

Sunitinib versus Interferon (IFN) in Previously Untreated mRCC

Endpoint	Sunitinib (n = 335)	IFN (n = 327)	*p*-value
Progression-free survival	11 months	5 months	<0.001
Overall response	31%	6%	<0.001
Complete response	0	0	—
Partial response	31%	6%	—
Stable disease	48%	49%	—

SOURCE: Motzer RJ et al. *N Engl J Med* 2007;356(2):115-24. **Abstract**

levels that were administered to heavily pretreated patients (Atkins 2004). The response rate was approximately 10 percent, but many patients experienced stabilization of disease, with a median progression-free survival of six months and an overall survival of approximately 12 months (Atkins 2004).

These results were better than for the historical control group, and subset analyses indicated that patients with poor-risk disease — according to the Memorial Sloan-Kettering classification — received the most benefit.

This led to a large, pivotal, Phase III trial of temsirolimus versus interferon alpha versus the combination as first-line treatment for patients with poor-risk features (Hudes 2007). The study was not confined to clear cell carcinoma and included patients with other renal cancer histologies. The second interim analysis demonstrated an improvement in survival for temsirolimus over interferon alpha or the combination of temsirolimus and interferon (Hudes 2007; [4.1]).

Track 15

DR LOVE: Over the past three to four years, how much improvement have you observed in survival and quality of life in the metastatic setting?

DR MOTZER: The discovery of targeted therapies represents dramatic progress in this disease. In renal cancer, we anticipate a situation similar to what we see in several of the other types of cancer in which a patient may benefit from one of these targeted therapies for a time, then experience progression. We'll be able to offer the patient a second, a third and potentially a fourth therapy. I believe we will see a dramatic change in overall survival for patients with metastatic renal cancer using multiple targeted therapies. ■

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Motzer RJ et al. **Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma.** *J Clin Oncol* 2006a;24(1):16-24. **Abstract**

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

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**

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

Daniel J George, MD

Dr George is Associate Professor of Medicine and Surgery and Director of Genitourinary Oncology at Duke Medical Center in Durham, North Carolina.

Tracks 1-18

Select Excerpts from the Interview

Track 2

DR LOVE: Can you discuss the available clinical research data for bevacizumab in RCC?

DR GEORGE: A trial by Jim Yang at the NCI was one of the first proof-of-concept studies. In patients who had failed interleukin-2, bevacizumab at 10 mg/kg every two weeks almost doubled the duration of progression-free survival compared to placebo. They were able to show that this real, dramatic

change in the natural history of the disease was accompanied by relatively few patients achieving a partial response (Yang 2003; [1.2]).

In the US, the CALGB conducted a large Phase III study (CALGB-90206) in which we compared bevacizumab with interferon to interferon alone. Those results showed a dramatic improvement in the duration of progression-free survival with the addition of bevacizumab (Rini 2008; [2.1]). In the CALGB study, the median time to progression for interferon alone was 5.2 months, and it was 8.5 months for interferon with bevacizumab (Rini 2008; [2.1]), which is similar to what we saw in the Roche study (AVOREN; [Escudier 2007; 2.2]).

In Europe, a similarly designed study (AVOREN) that included a placebo control — interferon/placebo versus interferon/bevacizumab — demonstrated similar results. An approximately 80 percent improvement was evident in median duration of progression-free survival, from 5.4 months for interferon/placebo to 10.2 months for interferon/bevacizumab (Escudier 2007; [2.2]). Now we have two large, multicenter, Phase III studies showing a dramatic improvement in progression-free survival with bevacizumab.

2.1

CALGB-90206: A Phase III Randomized Trial of Bevacizumab and Interferon Alpha for Patients (N = 732) with Previously Untreated mRCC

	Bevacizumab + interferon	Interferon
Median time to progression	8.5 months*	5.2 months
Overall response rate	25.5%*	13.1%
Grade III hypertension	9%	0%
Anorexia	17%	8%
Fatigue	35%	28%
Proteinuria	13%	0%

* $p < 0.0001$

"Bevacizumab plus IFN produces a superior PFS and ORR in untreated metastatic RCC versus IFN monotherapy. Toxicity is greater in the combination arm."

SOURCE: Rini BI et al. *Proc ASCO Genitourinary Cancers Symposium* 2008;**Abstract 350**.

Tracks 3-4

DR LOVE: What about bevacizumab monotherapy for a patient with asymptomatic or minimally symptomatic metastatic disease?

DR GEORGE: It probably has the least toxic profile. We don't see hand-foot syndrome with bevacizumab. We also don't see diarrhea or gastrointestinal toxicities. Fatigue is probably less significant than what we see with the other targeted agents. Bevacizumab is probably the least toxic as a single agent in terms of being able to have an anti-angiogenic biologic effect, delay the progression of disease and change the natural history.

2.2

AVOREN: A Phase III Double-Blind, Randomized Study of Bevacizumab and Interferon Alpha-2a for Patients with Previously Untreated mRCC

Efficacy	Bevacizumab + interferon (n = 306)	Placebo + interferon (n = 289)	*p*-value
Median duration of PFS	10.2 months	5.4 months	0.0001
Overall response rate	31%	13%	0.0001
Duration of response	13.5 months	11.1 months	NR

PFS = progression-free survival; NR = not reported

"...The combination of bevacizumab with interferon alfa in patients with metastatic clear-cell renal cell carcinoma produces significant and clinically meaningful improvements in progression-free survival and overall response rates."

SOURCE: Escudier B et al; AVOREN Trial investigators. *Lancet* 2007;370(9605):2103-11. **Abstract**

The key questions are, how much more effective are these other regimens, and does interferon sufficiently improve the progression-free survival when combined with bevacizumab to justify the months of interferon toxicity? These questions will be difficult to answer in a clinical trial. That's where the art of medicine comes in for a practicing clinician — determining to what extent your patient can tolerate the side-effect profile and gain a benefit.

Some patients tolerate the combination well, but I believe they are the minority. Physicians may decide to try a combination of interferon/bevacizumab and discontinue or reduce the dose of interferon if and when toxicities occur. They may also decide to start with bevacizumab alone, and if patients are faring well, they may try administering interferon. These concepts aren't proven in a clinical trial setting but can be extrapolated from the existing data.

DR LOVE: Do you have a sense of how much toxicity the cytokines add to bevacizumab in this situation?

DR GEORGE: I believe it would be substantial. Approximately 80 percent of the toxicities — fever, chills, weight loss, cytopenias, et cetera — are driven by the cytokines. With bevacizumab alone, very few of those side effects are evident. The side effects primarily seen with bevacizumab include fatigue, hypertension and proteinuria, which patients can tolerate well in a chronic setting without a lot of symptoms. I believe many physicians in the community will attempt to use bevacizumab monotherapy.

DR LOVE: How much is the cytokine contributing to the efficacy that is seen with the combination?

DR GEORGE: We don't have randomized data to answer the question definitively. I will say that in both of these Phase III studies — CALGB (Rini 2008; [2.1]) and AVOREN (Escudier 2007; [2.2]) — the partial response rate was in the 20 to 25 percent range for the combination, which is higher than we've seen in any Phase III study of interferon alone, and it is higher than what

we've seen with bevacizumab alone in those relatively small Phase II studies (Bukowski 2007; Yang 2003). I believe some effect of the cytokines is interacting with bevacizumab, but to what extent does that justify the toxicity?

Track 12

DR LOVE: Setting cost and reimbursement issues aside and focusing on risk-benefit along with clinical science, could you discuss your current algorithm for first- and second-line therapy for patients with metastatic disease?

DR GEORGE: My answers today are different than they were one year ago, and they are likely to be different a year from now. When I first see my patients, I "size them up" as having good-, intermediate- or poor-risk disease.

For a young, healthy patient with asymptomatic, low-volume disease who experienced a delay from the original diagnosis to the time of metastasis (ie, good-risk disease), I may discuss high-dose interleukin-2. Although we don't have a durable, long-term, disease-free control or cure rate, we know that a subset of patients will have a complete response. I believe it's fair for patients to at least hear about interleukin-2, but I don't push anybody toward it. Interleukin-2 is an extremely toxic approach, and you need motivated patients in order to get them through the treatment.

Then we'll talk about some of our other agents. The agent we have the best data with in the first-line setting is sunitinib. In a Phase III study, the subpopulation with good-risk disease showed a dramatic progression-free survival benefit with sunitinib compared to interferon. The hazard ratio was 0.37 (Motzer 2007). So that's a population in which I'll either consider watchful waiting or sunitinib.

Bevacizumab at every other-week dosing would be an alternative. In a patient population that may be on a drug for a year or more, we'll talk about bevacizumab. So in that population, we'll start with those two agents. Sorafenib and temsirolimus are agents I'd consider in the second- or third-line setting. ■

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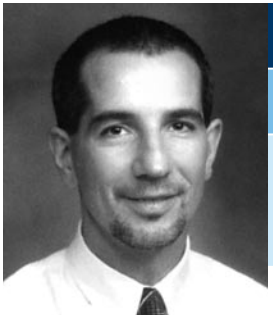
Rini BI et al. **CALGB 90206: A phase III trial of bevacizumab plus interferon-alpha versus interferon-alpha monotherapy in metastatic renal cell carcinoma.** *Proc ASCO Genitourinary Cancers Symposium* 2008;**Abstract 350**.

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 J Amato, DO

Dr Amato is Medical Director of the Genitourinary Oncology Program at The Methodist Hospital Research Institute in Houston, Texas.

Tracks 1-18

Select Excerpts from the Interview

Track 1

DR LOVE: What's your take on the safety and toxicity issues with the major options for first-line treatment of metastatic RCC?

DR AMATO: That's a good question. Let's break it down. The predominant side effect with sunitinib is fatigue, thus the built-in break — four weeks on, two weeks off. Additional side effects occur, from skin reactions to gastrointestinal reactions, and occasionally you'll obtain a hematologic profile with a decrease in counts. Those patients need the two-week rest period.

The clear issue with sorafenib is skin reactions associated with hand-foot syndrome. With both of these drugs, if you begin manipulating by lowering the dose to adjust for side-effect toxicity, you tend to lose efficacy. So you need to maintain at the approved doses.

Bevacizumab as a single agent is more manageable. Patients may exhibit some hypertension and proteinuria, but those are more manageable. With the addition of interferon to bevacizumab, the side-effect profile remains similar. If one evaluates this strictly from a tolerability standpoint, it would be fair to make the statement that interferon/bevacizumab is better tolerated than the oral TKIs.

DR LOVE: What about efficacy?

DR AMATO: It is unfair to say one is better than the other without conducting head-to-head trials. But if you compare across the board, they are similar. Phase II and Phase III data with sunitinib indicate anywhere from 30 to 40 percent activity, with an additional disease-stabilization portion (Motzer 2006a, 2007).

In trials evaluating sorafenib, activity is somewhere between five and 10 percent, but again with that stability portion (Escudier 2007c). Studies of interferon/bevacizumab reported approximately a 30 percent tumor response rate, again with a stability fraction (Escudier 2007b). With regard to progression-free survival, they're all between five and 10 months.

Track 4

DR LOVE: Can you talk about your presentation at ASCO evaluating dose escalation of sorafenib (Amato 2007; [3.1])?

DR AMATO: The trial was for patients with clear cell component mRCC, who were started on sorafenib at 400 milligrams BID then had the dose escalated according to a prescribed schedule.

The study was based on Phase I data suggesting that at higher doses, sorafenib exhibited more activity, leading to the hypothesis that you might have more kinase inhibition at higher doses.

We reported a 16 percent complete response rate among 44 patients. Seven of 44 patients had a complete response, and another 17 had a partial response — a 55 percent objective response. The progression-free survival median was 8.4 months, which suggests that we now have a complete response rate population and partial response rate population similar to what we know of already, simply by increasing the dose.

DR LOVE: Do you believe that's a reasonable strategy to implement currently in a clinical setting?

DR AMATO: Not at the present time. We are confirming the data. All the complete responders are approaching 15 to 24 months now, and we have added another 30 patients. Tune in at the next ASCO, and we will have the answers. ■

3.1

A Phase II Trial of Intrapatient Dose-Escalated Sorafenib for Patients with mRCC

	N (%)	Months (95% CI)
Median overall survival	44 (100)	11.47 (4.27-17.37)
Median progression-free survival		
Overall population	44 (100)	8.43 (3.00-17.37)
Complete* and partial responders	24 (55)	9.55 (3.00-17.37)
Stable disease ≥ 6 months	9 (20)	8.73 (6.00-10.73)

* For all complete responders on trial (n = 7), no progression of disease was seen at time of follow-up (17.37 months), and patients were maintained at the full 1,600-mg dose.

Comments from Dr Amato's ASCO presentation

"It's clear that dose escalated sorafenib is well tolerated when given twice daily by oral administration. Ninety-three percent of our patients were able to be dose escalated to either 1200 or 1600 mg per day. There was a high level of antitumor activity demonstrated by a 55% complete (CR) and partial (PR) response rate in patients with metastatic RCC. Antitumor activity was suggested by a prolonged median time to progression of 8.4 months, and that is likely to improve as these PRs and CRs continue to receive medication. There was activity demonstrated in those 43% who failed prior cytokine therapy. So clearly the blocking of multiple pathways that we're already familiar with — VEGF, PDGF, C-KIT and FLT3 — has a role. There's a clear role for intrapatient dose escalation.

We have other colleagues now who are getting ready to confirm this data at Nebraska, Stanford and New Jersey and they will each put on 15-20 patients. We're going to continue adding another 30 patients to further evaluate the pharmacologic PK and determine what's actually taking place."

SOURCE: Amato RJ et al. *Proc ASCO* 2007;**Abstract 5026**.

SELECT PUBLICATIONS

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Escudier B et al; AVOREN Trial Investigators. **Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: A randomised, double-blind phase III trial.** *Lancet* 2007b;370(9605):2103-11. **Abstract**

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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

Janice P Dutcher, MD

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

Tracks 1-18

Select Excerpts from the Interview

Track 1

DR LOVE: Can you talk about the temsirolimus/interferon alpha data that were reported at ASCO 2006?

DR DUTCHER: The study of temsirolimus versus interferon versus the combination in patients with poor-risk renal cell cancer was initially presented at ASCO 2006 (Hudes 2006, 2007; [4.1, 4.2]). The poor-risk features were

based on criteria from Sloan-Kettering (Motzer 2002) and included nephrectomy status, high serum lactate dehydrogenase levels, anemia, hypercalcemia and rapid time from diagnosis of primary RCC to mRCC and features that reflected a likelihood of rapid disease progression.

The study demonstrated a significant improvement in progression-free survival and overall survival for temsirolimus compared to interferon (4.1). This finding suggests that in patients with poor-risk disease, immunotherapy cannot catch up to the disease process, whereas targeting a different pathway might be effective.

We went back and evaluated the data, and a significant number of patients did not have clear cell renal cancer (Dutcher 2007). These patients had different histologies, mostly papillary or undifferentiated mRCC, and they benefited from temsirolimus significantly more than from interferon, which supports our belief that immunotherapy is not as effective in nonclear cell mRCC.

4.1

Temsirolimus, Interferon Alpha (IFN) or the Combination for Previously Untreated, Poor-Risk mRCC

	IFN (n = 207)	Temsirolimus (n = 209)	IFN + temsirolimus (n = 210)
Overall survival	7.3 mo	10.9 mo*	8.4 mo
Progression-free survival	1.9 mo	3.8 mo	3.7 mo
Time to treatment failure	1.9 mo	3.8 mo	2.5 mo
Objective response†	4.8%	8.6%	8.1%

* For comparison of temsirolimus versus IFN, hazard ratio for death was 0.73; $p = 0.008$.

† Includes only patients who underwent tumor assessment after the baseline assessment (IFN, n = 153; temsirolimus, n = 192; IFN + temsirolimus, n = 168)

"The principal finding was that, as compared with interferon alone, treatment with temsirolimus was associated with a moderate prolongation of overall survival in patients with advanced renal-cell carcinoma and a poor prognosis."

SOURCE: Hudes G et al; Global ARCC Trial. *N Engl J Med* 2007;356(22):2271-81. **Abstract**

4.2

Select Grade III/IV Adverse Events Occurring in at Least 20 Percent of Patients in Any Group

Adverse event	IFN (n = 200)	Temsirolimus (n = 208)	IFN + temsirolimus (n = 208)
Asthenia	26%	11%	28%
Anemia	22%	20%	38%
Dyspnea	6%	9%	10%
Infection	4%	5%	11%
Hyperglycemia	2%	11%	6%
Neutropenia	7%	3%	15%

SOURCE: Hudes G et al; Global ARCC Trial. *N Engl J Med* 2007;356(22):2271-81. **Abstract**

Tracks 6-7

DR LOVE: What factors do you take into consideration when deciding on first-line therapy in the metastatic setting for clear cell RCC?

DR DUTCHER: We still administer high-dose interleukin-2 to patients who seem likely to respond to this therapy, and some patients have durable complete responses lasting several years.

My own approach is to screen patients to determine whether they are candidates for high-dose interleukin-2 and discuss that therapy along with targeted therapy options. If possible, I prefer to enter patients on a clinical trial for first-line therapy in the metastatic setting.

In cases for which we need tumor shrinkage right away — for example, an endobronchial tumor that's causing atelectasis — sunitinib would be more effective because its shrinkage rate is higher than other first-line options.

At present we do not have a lot of information on first-line temsirolimus. However, based on the available data, it would be a good choice for patients with poor-risk disease (Hudes 2007).

DR LOVE: Interleukin-2 is typically considered for use in younger, healthier patients. Is this your practice?

DR DUTCHER: I base my decision on physiology as opposed to age. The patients I encourage to receive interleukin-2 are those with lung-only metastasis and good pulmonary and cardiac function. I treat patients in their late sixties or early seventies who have fairly limited metastatic disease.

For patients with rapidly growing disease, I do not use immunotherapy. Those patients need targeted therapy because it provides a better chance to stop the disease. Interleukin-2 is more appropriate for patients with more typical, slow-growing, indolent mRCC. ■

SELECT PUBLICATIONS

Atkins M et al. **Carbonic anhydrase IX expression predicts outcome of interleukin 2 therapy for renal cancer.** *Clin Cancer Res* 2005;11(10):3714-21. **Abstract**

Dutcher JP et al. **Correlation of survival with tumor histology, age, and prognostic risk group for previously untreated patients with advanced renal cell carcinoma (adv RCC) receiving temsirolimus (TEMSR) or interferon-alpha (IFN).** *Proc ASCO* 2007;**Abstract 5033**.

Hudes G et al; Global ARCC Trial. **Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma.** *N Engl J Med* 2007;356(22):2271-81. **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**.

Motzer RJ et al. **Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma.** *J Clin Oncol* 2002;20:289-96. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The overall response rate with bevacizumab monotherapy among patients with mRCC previously treated with interleukin-2 was _____ percent.**
   a. One
   b. Five
   c. 10
   d. 30

2. **The TARGET trial demonstrated a statistically significant improvement in _____ with sorafenib compared to placebo among patients with previously untreated mRCC.**
   a. Overall survival
   b. Progression-free survival
   c. Both a and b

3. **A large Phase III trial of sunitinib versus interferon for patients with previously untreated mRCC demonstrated significant improvements in _____ among patients treated with sunitinib.**
   a. Overall survival
   b. Progression-free survival
   c. Both a and b

4. **Two Phase III randomized trials have shown that bevacizumab with interferon improves _____ compared to interferon alone.**
   a. Overall survival
   b. Cancer-specific survival
   c. Progression-free survival
   d. All of the above

5. **In the AVOREN trial of interferon with or without bevacizumab for mRCC, overall response was _____ percent among patients who received bevacizumab/interferon.**
   a. 13
   b. 20
   c. 31
   d. 40

6. **In the AVOREN trial, progression-free survival among patients who received interferon with bevacizumab was double that among patients who received interferon alone.**
   a. True
   b. False

7. **Both sorafenib and sunitinib may lead to hand-foot skin reactions in patients with RCC.**
   a. True
   b. False

8. **In Dr Amato and colleagues' Phase II dose-escalation trial of sorafenib, the highest dose administered was _____.**
   a. 400 milligrams daily
   b. 800 milligrams daily
   c. 1,600 milligrams daily
   d. 3,200 milligrams daily

9. **The objective response rate in the study conducted by Dr Amato and colleagues of dose-escalated sorafenib for patients with mRCC was _____.**
   a. 21 percent
   b. 33 percent
   c. 56 percent

10. **The Phase III study of temsirolimus (TEMSR) or interferon alpha (IFN) or the combination of TEMSR and IFN in the first-line treatment of poor-risk advanced RCC demonstrated a significant improvement in _____.**
    a. Disease-free survival
    b. Overall survival
    c. Both a and b
    d. None of the above

11. **Poor-risk features in the Phase III study of TEMSR, IFN or the combination for patients with poor-risk advanced disease included _____.**
    a. No nephrectomy
    b. High LDH
    c. Anemia
    d. All of the above
    e. None of the above

12. **In the SELECT study, patients eligible to participate will receive high-dose _____ as therapy.**
    a. Sunitinib
    b. Temsirolimus
    c. Interleukin-2

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Renal Cell Cancer Update — Issue 1, 2008

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Phase III trial results (AVOREN, CALGB-90206) for first-line bevacizumab/interferon 4 3 2 1

TARGET trial results: First-line sorafenib versus placebo 4 3 2 1

Intrapatient dose escalation of sorafenib . . . 4 3 2 1

First-line temsirolimus for poor-risk mRCC 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Phase III trial results (AVOREN, CALGB-90206) for first-line bevacizumab/interferon 4 3 2 1

TARGET trial results: First-line sorafenib versus placebo 4 3 2 1

Intrapatient dose escalation of sorafenib . . . 4 3 2 1

First-line temsirolimus for poor-risk mRCC 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: . . . . . .

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: . . . . . .

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: . . . . . .

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will:

- Apply an understanding of the biology underlying clear cell RCC, including inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene and the pathway leading to VEGF overexpression, to therapeutic decision-making. . . . . 4 3 2 1 N/M N/A
- Construct management strategies for patients with advanced RCC, considering safety and efficacy profiles for targeted biologic therapies inhibiting VEGF, PDGF and EGF receptors. . . . . 4 3 2 1 N/M N/A
- Evaluate the impact of pathologic grade on the selection of therapies and clinical outcomes in RCC, assess molecular targets believed to have clinical relevance in RCC and apply this information to clinical practice. . . . . 4 3 2 1 N/M N/A
- Develop a therapeutic approach for the sequencing and duration of treatment with targeted biologic therapies for patients with RCC. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about participation in clinical trials in the adjuvant and metastatic settings. . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

. . . . . .

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

.....

May we include you in future assessments to evaluate the effectiveness of this activity?

☐ Yes ☐ No

PART TWO — Please tell us about the faculty for this educational activity

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Faculty	Knowledge of subject matter	Effectiveness as an educator
Robert J Motzer, MD	4 3 2 1	4 3 2 1
Daniel J George, MD	4 3 2 1	4 3 2 1
Robert J Amato, DO	4 3 2 1	4 3 2 1
Janice P Dutcher, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

Name:..... Specialty:.....

Degree:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ BS ☐ RN ☐ PA ☐ Other .....

Medical License/ME Number:..... Last 4 Digits of SSN (required):.....

Street Address:..... Box/Suite:.....

City, State, Zip:.....

Telephone:..... Fax:.....

Email:.....

Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature:..... Date:.....

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at www.RenalCellCancerUpdate.com/CME.

RCCU108

Renal Cell Cancer™

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U P D A T E

This program is supported by educational grants from
Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc
and Genentech BioOncology.

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Sponsored by Research To Practice.

Last review date: April 2008
Release date: April 2008
Expiration date: April 2009
Estimated time to complete: 3 hours