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Renal Cell Cancer™

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

EDITOR

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INTERVIEWS

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CME Certified

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Renal Cell Cancer Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Advances in the biologic understanding of renal cell cancer and the emergence of clinical trial data with targeted therapeutic agents have resulted in the availability of novel treatment strategies for this challenging disease. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these rapidly evolving data sets. To bridge the gap between research and patient care, Renal Cell Cancer Update utilizes one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME activity assists medical oncologists with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Use prognostic tools to estimate risk of disease recurrence, and communicate these findings to patients with resected renal cell cancer (RCC).
- Demonstrate an understanding of the biology of clear cell RCC, including inactivation of the von Hippel-Lindau (VHL) tumor-suppressor gene and the pathway leading to VEGF overexpression.
- Develop an approach for the sequencing of therapies for advanced RCC, incorporating biologic response modifiers, tyrosine kinase inhibitors (TKIs), anti-VEGF antibodies and mTOR inhibitors.
- Inform patients about the side effects associated with various therapeutic options when recommending systemic treatment for advanced RCC.
- Critically evaluate emerging clinical trial data with second-generation TKIs, and appraise their impact on the RCC treatment algorithm.
- Counsel appropriately selected patients with RCC about participation in ongoing clinical trials in the adjuvant and metastatic settings.

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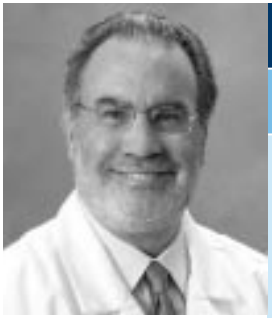


INTERVIEW

Robert A Figlin, MD

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

Tracks 1-19

Select Excerpts from the Interview

Track 3

DR LOVE: Would you provide an update on the Intergroup adjuvant trial (ECOG-E2805) evaluating sunitinib versus sorafenib versus placebo?

DR FIGLIN: ECOG-E2805 is entering the last phases of accrual — a 1,300-patient target accrual with almost 1,200 patients currently on the trial. The trial compares standard-dose sunitinib (four weeks on, two weeks off) to standard-dose sorafenib (two pills twice daily for six weeks) to placebo (1.1).

Considering the absence of any current data with these targeted agents in the adjuvant setting, when I have a patient with a significant but not a 100 percent chance of cure with surgery alone, I have a candid conversation with that patient about the risks and benefits of these agents. Patients are now asking questions such as, "Do I want to be treated now on a clinical research trial? Do I want to take my chances, wait until later and receive therapy if the cancer comes back? And in balance, what should I do?" Until we have definitive answers about the true benefits of adjuvant therapy, my belief is that the standard treatment is careful follow-up.

1.1

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

Target Accrual: 1,332
Current Accrual: 1,274 (4/18/09)
Date Activated: April 24, 2006

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

Study Contacts

Eastern Cooperative Oncology Group
Naomi Balzer-Haas, MD, Protocol Chair
Keith Flaherty, MD, Protocol Co-Chair
Robert Uzzo, MD, Protocol Co-Chair
Cancer and Leukemia Group B
Christopher Kane, MD, Protocol Chair
Southwest Oncology Group
Christopher Wood, MD, Protocol Chair
NCIC-Clinical Trials Group
Michael Jewett, MD, Protocol Chair

SOURCES: NCI Physician Data Query, April 2009; www.ctsu.org.

Tracks 7, 12

DR LOVE: Would you discuss the presentation at ASCO 2008 of the Phase II trial evaluating pazopanib for patients with metastatic RCC?

DR FIGLIN: Tom Hutson was the first author and I was the senior author, and we're hopeful that this manuscript will be accepted because it is now under review. This trial evaluated pazopanib — a second-generation VEGF tyrosine kinase inhibitor (TKI) — with promising results. Progression-free survival and overall response rate were comparable to what one would expect from the other TKIs (Hutson 2008; [1.2]). A Phase III trial comparing pazopanib to placebo will soon be reported, and another Phase III trial comparing pazopanib to sunitinib is ongoing, with the aim of demonstrating noninferiority in efficacy, with perhaps a toxicity advantage.

We also wanted to move one step further. We performed biomarker analysis in circulating factors and tumor tissue in an attempt to identify predictors of benefit. One factor we reported on was soluble VEGF receptor 2 (sVEGFR2), which is easy to measure in the serum. Based on these Phase II trial results, sVEGFR2 appears to be a predictor of response and progression-free survival (1.2).

Another factor we examined was the von Hippel-Lindau (VHL) gene, which occurs in patients with the genetic disease called von Hippel-Lindau syndrome and occurs in sporadic kidney cancer in a majority of patients with clear cell tumors. This gene drives a specific biology — the activation of hypoxia-inducible factor (HIF) alpha, whose downstream targets activate a series of events, including tumor angiogenesis, which is the one we are currently most interested in blocking.

Patients with VHL abnormalities seem to be perfect candidates to benefit from a TKI, so we evaluated this prospectively and found that approximately 90 percent of people have either a mutation or a hypermethylation of the VHL gene. However, we were unable to distinguish a correlation between VHL status and clinical response to these targeted agents, regardless of whether patients had wild-type, mutated or hypermethylated disease. This means that VHL status is probably not a good discriminator between which patients should or should not receive pazopanib.

1.2

Phase II Trial of Pazopanib for Patients with mRCC: Efficacy and Biomarker Analysis Results

Efficacy	Pazopanib	95% CI
Median progression-free survival	11.9 months	10.1-13.9
Response rate (CR + PR)	34.7%	28.4-40.9

Biomarker analysis	sVEGFR2 % change from baseline			
	>31% decrease (n = 92)	≤31% decrease (n = 91)	Hazard ratio (95% CI)	*p*-value
Progression-free survival	12.0 months	10.9 months	1.49 (1.00-2.24)	0.050

SOURCE: Hutson TE et al. *Proc ASCO* 2008;**Abstract 5046**.

Axitinib is another VEGFR TKI. Brian Rini and Olivier Rixe have reported extensively on it (Rixe 2007). Preclinical studies indicate that not as much axitinib is needed to destroy cells in culture as some of the other agents, and that observation has led to the belief that this may be a powerful TKI for patients with RCC (Hu-Lowe 2008).

Axitinib is now being compared to sorafenib in the second-line setting for patients whose disease progresses after one prior systemic first-line regimen for metastatic RCC to ascertain the feasibility of following one TKI with another TKI as salvage therapy. I believe that's a valuable study.

This will set up an interesting dialogue because we now know that everolimus is widely used, based on the Phase III publication in *The Lancet* reporting on patients whose disease progressed on VEGFR targeted therapy (sunitinib or sorafenib). Everolimus inhibits a completely different pathway — the mTOR pathway. The authors reported a progression-free survival of 4.6 months with everolimus compared to 1.9 months with placebo (Motzer 2008). Many of us would now like to have an analysis evaluating disease progression on a VEGFR TKI and to know whether it is best to try another VEGFR TKI or move to a different class of agents, such as an mTOR inhibitor.

Track 14

DR LOVE: Can you discuss the ongoing Phase III trial comparing bevacizumab and interferon to bevacizumab and everolimus?

DR FIGLIN: Good data are already available with the combination of bevacizumab and interferon, with reports indicating that the combination is well tolerated and capable of doubling progression-free survival when compared to interferon alone (Escudier 2007b; Rini 2008). With the Phase III trial (NCT00719264) comparing bevacizumab/interferon to bevacizumab/everolimus, we want to ascertain whether we can add to that with horizontal or vertical inhibition. If we inhibit the VEGF ligand and mTOR at the same time, is that better than inhibiting only the VEGF ligand and then at the time of disease progression treating with some other agent?

Tracks 15-16

DR LOVE: How would you compare the side effects and toxicities of the new agents in RCC, and how does that figure into your approach for the patients with asymptomatic metastatic disease?

DR FIGLIN: We are not yet able to assert that treatments A, B and C are equally efficacious so let's simply pick the least toxic regimen. I believe that at the moment we're still motivated by efficacy, and therefore you have a balanced conversation with the patient about sunitinib, about bevacizumab and interferon and about sorafenib, understanding that sorafenib may be less toxic but the randomized data with untreated patients suggest that it's also less beneficial.

For the overwhelming majority of patients, bevacizumab is better tolerated than the oral TKIs, and we have extensive experience with it. It is administered to patients with colorectal cancer, breast cancer and lung cancer, with a few caveats.

However, some of the severe toxicities associated with bevacizumab can be life threatening.

DR LOVE: What are your thoughts about bevacizumab monotherapy for patients with RCC?

DR FIGLIN: I believe that's a somewhat complicated discussion. We published findings in the *Journal of Clinical Oncology*, and we were unable to demonstrate that bevacizumab/erlotinib was any different from bevacizumab alone (Bukowski 2007). Other large Phase III trials — the CALGB-90206 trial and the AVOREN trial — compared bevacizumab/interferon to interferon alone (Escudier 2007b; Rini 2008).

I advise patients and physicians to start with bevacizumab/interferon based on peer-reviewed data. You modify the interferon dose in the case of toxicity, and if at the end of the day you're left treating a patient with bevacizumab alone because he or she can't tolerate the interferon, you recognize that's still likely to benefit the patient. ■

SELECT PUBLICATIONS

Bukowski RM et al. **Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer.** *J Clin Oncol* 2007;25(29):4536-41.

Choueiri TK et al. **von Hippel-Lindau gene status and response to vascular endothelial growth factor targeted therapy for metastatic clear cell renal cell carcinoma.** *J Urol* 2008;180(3):860-5.

Escudier B et al. **A randomized, controlled, double-blind phase III study (AVOREN) of bevacizumab/interferon-α2a vs placebo/interferon-α2a as first-line therapy in metastatic renal cell carcinoma.** *Proc ASCO* 2007a;**Abstract 3**.

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.

Hu-Lowe DD et al. **Nonclinical antiangiogenesis and antitumor activities of axitinib (AG-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3.** *Clin Cancer Res* 2008;14(22):7272-83.

Hutson TE et al. **Biomarker analysis and final efficacy and safety results of a phase II renal cell carcinoma trial with pazopanib (GW786034), a multi-kinase angiogenesis inhibitor.** *Proc ASCO* 2008;**Abstract 5046**.

Motzer RJ et al; RECORD-1 Study Group. **Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial.** *Lancet* 2008;372(9637):449-56.

Rini BI et al. **Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206.** *J Clin Oncol* 2008;26(33):5422-8.

Rixe O et al. **Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: A phase II study.** *Lancet Oncol* 2007;8(11):975-84.

INTERVIEW

Ronald M Bukowski, MD

Dr Bukowski is Emeritus Staff and Consultant at the Cleveland Clinic Taussig Cancer Center and Professor of Medicine at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University in Cleveland, Ohio.

Tracks 1-18

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the data with pazopanib that your group presented at the 2008 ASCO meeting?

DR BUKOWSKI: Pazopanib is a small-molecule inhibitor of the VEGF receptors. It is similar to sunitinib but might have fewer off-target effects, so it is of interest in that it may have an improved toxicity profile.

It has been studied in some detail during the past three to four years. The first study — reported two years ago at ASCO by my colleague Tom Hutson —

was a randomized discontinuation trial, in which oral pazopanib was administered daily to patients with advanced RCC (Hutson 2007; [2.1]).

The randomization was stopped early because pazopanib was so effective that a randomized discontinuation approach could not be continued — you wouldn't want to stop the drug for a patient who was benefiting (Hutson 2007).

In a cohort of approximately 200 patients, they found a respectable response rate of about 35 percent and progression-free survival was approximately 12 months. These data suggest that pazopanib may be equivalent to sunitinib. If pazopanib indeed has less toxicity, then it will be useful (Hutson 2008a).

We're waiting to hear the results from a randomized trial of pazopanib versus placebo for more than 400 patients, predominantly from Europe. This pivotal trial will allow pazopanib to be submitted to the FDA for approval as a treatment for advanced RCC.

Pazopanib may have a better toxicity profile than sunitinib, but it will be difficult to know that unless they are compared directly. A large study will compare sunitinib to pazopanib for patients with previously untreated metastatic RCC. This study will test for noninferiority and will evaluate whether pazopanib has less toxicity or a better side-effect profile than sunitinib in a randomized, controlled setting.

2.1

Efficacy and Side Effects of Oral Pazopanib in Patients with Advanced RCC

Final efficacy analysis

	Independent review (n = 225)	Investigator review (n = 225)
Response rate (CR + PR)	34.7%	33.8%
Stable disease	44.5%	42.2%
Progression-free survival	11.9 months	9.9 months

Select pazopanib-related adverse events (n = 225)

	Any grade	Grade III	Grade IV
Diarrhea	59%	4%	0%
Hair color changes	43%	0%	0%
Hypertension	40%	8%	0%
Nausea	37%	<1%	0%
Fatigue	37%	4%	0%
Vomiting	15%	<1%	0%
Rash	12%	<1%	0%
Hand-foot syndrome	12%	2%	0%

CR = complete response; PR = partial response

SOURCE: Hutson TE et al. *Proc ASCO* 2008a;**Abstract 5046**.

Track 6

DR LOVE: If sunitinib were compared to bevacizumab or to bevacizumab/interferon in a randomized trial, what do you believe we would observe in terms of efficacy and quality of life?

DR BUKOWSKI: Applying the data that I am aware of with these three approaches, I believe that sunitinib would have the highest response rate (Motzer 2007), and the response rate with bevacizumab/interferon would be respectable (Escudier 2007; Rini 2008). For these two approaches, the progression-free survival would likely be similar. The bevacizumab-alone arm would likely have a lower response rate, somewhere around 10 percent for previously untreated patients (Yang 2003).

Whether progression-free survival would also be lower remains to be seen. Individuals may start with the combination of interferon and bevacizumab and then continue with bevacizumab alone, in the same manner as using chemotherapy and bevacizumab and continuing maintenance bevacizumab. Oncologists are sometimes driven by their previous experience with drugs. Bevacizumab alone is the best tolerated of all of these agents, so it will be desirable to introduce it into therapy. The important factor will be ensuring that we don't compromise efficacy.

Tracks 11-13

DR LOVE: Would you comment on the use of sunitinib and sorafenib in elderly patients with advanced renal cell cancer?

DR BUKOWSKI: In the TARGET study, comparing sorafenib versus placebo for metastatic disease, patients age 70 and older who received sorafenib demonstrated equivalent progression-free survivals as those younger than age 70 and their toxicities did not appear to be any worse (Eisen 2008).

Sunitinib can also be used for elderly patients with advanced disease. Much of the information we have on sunitinib in this population comes from clinical experience. When treating patients with this agent, one simply needs to be aware of its toxicity profile. The major side effect is fatigue, experienced mainly during the last two weeks of the treatment cycle.

DR LOVE: How do you manage the fatigue?

DR BUKOWSKI: One can either increase the break from two weeks to three or decrease the dose from 50 to 37.5, then 25 milligrams (Hutson 2008b; [2.2]). We start to see more acceptable levels of fatigue around 37.5 or 25 milligrams. The fatigue doesn't dissipate, but it's less problematic and the patients learn to live with and manage it.

We don't know the mechanism behind the fatigue. Nor have I found any medication that effectively alters it. Patients' descriptions of the fatigue don't

differ from that described with interferon, for example. The fatigue is such that they sometimes have difficulty carrying on normal daily activities.

We always caution clinicians to be certain that the fatigue is secondary to sunitinib and rule out other possible causes, such as severe anemia or hypothyroidism. Also, when a patient complains, "I just don't want to get out of the chair," one needs to consider depression as a contributing factor. ■

2.2

Sunitinib: Treatment and Dose Adjustments in the Treatment of Metastatic Renal Cell Carcinoma (RCC)

"The recommended dose for sunitinib for patients with advanced RCC is one 50-mg oral dose daily, with or without food, on schedule 4/2. Most side effects are reversible and should not result in discontinuation of sunitinib. If necessary, toxicities may be managed through dose adjustments or interruptions.

A standard dose modification in 12.5-mg steps is recommended based on individual safety and tolerability: dose level 1, 50 mg for 4 weeks, 2 weeks off; dose level 2, 37.5 mg for 4 weeks, 2 weeks off; dose level 3, 25 mg for 4 weeks, 2 weeks off. Tumors tend to regrow during the 2-week break period or if plasma concentrations are too low for complete receptor inhibition. Discontinuation of sunitinib is indicated in the presence of clinical evidence of congestive heart failure and in patients with symptoms of pancreatitis or hepatic failure."

[Citations omitted]

SOURCE: Hutson TE et al. *Oncologist* 2008b;13(10):1084–96.

SELECT PUBLICATIONS

Eisen T et al. **Sorafenib for older patients with renal cell carcinoma: Subset analysis from a randomized trial.** *J Natl Cancer Inst* 2008;15;100(20):1454–63.

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* 2007;370(9605):2103–11.

Hutson TE et al. **Biomarker analysis and final efficacy and safety results of a phase II renal cell carcinoma trial with pazopanib (GW786034), a multi-kinase angiogenesis inhibitor.** *Proc ASCO* 2008a;**Abstract 5046**.

Hutson TE et al. **Targeted therapies for metastatic renal cell carcinoma: An overview of toxicity and dosing strategies.** *Oncologist* 2008b;13(10):1084–96.

Hutson TE et al. **Pazopanib (GW786034) is active in metastatic renal cell carcinoma (RCC): Interim results of a phase II randomized discontinuation trial (RDT).** *Proc ASCO* 2007;**Abstract 5031**.

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

Rini BI et al. **Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206.** *J Clin Oncol* 2008;26(33):5422–8.

Sloan B, Scheinfeld NS. **Pazopanib, a VEGF receptor tyrosine kinase inhibitor for cancer therapy.** *Curr Opin Investig Drugs* 2008;9(12):1324–35.

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.

INTERVIEW

Bruce G Redman, DO

Dr Redman is Professor of Medicine at the University of Michigan Medical Center in Ann Arbor, Michigan.

Tracks 1-11

Track 1	**Case discussion:** A 50-year-old woman who received high-dose interleukin-2 (IL-2) for clear cell mRCC
Track 2	Counseling patients about the benefits and risks associated with high-dose IL-2
Track 3	Achieving a complete remission with high-dose IL-2 in mRCC
Track 4	Toxicities experienced with high-dose IL-2
Track 5	**Case discussion:** A man who developed thyroiditis after treatment with high-dose IL-2 for mRCC
Track 6	Etiology and clinical presentation of thyroiditis related to high-dose IL-2
Track 7	Selection of patients for and clinical outcomes with high-dose IL-2 for mRCC
Track 8	Mechanism of action of IL-2
Track 9	Adoptive immunotherapy for RCC
Track 10	Combining targeted therapies for RCC
Track 11	Clinical use of bevacizumab for mRCC

Select Excerpts from the Interview

Tracks 2, 6-7

DR LOVE: What are the current available data on the efficacy of high-dose interleukin-2 (IL-2) for patients with metastatic RCC?

DR REDMAN: Approximately one out of every 10 well-chosen patients with clear cell carcinoma will experience a durable long-term complete response. Unfortunately, nine out of 10 patients will not.

Initially, the long-term complete remission rates were about six to seven percent, but that was before we subclassified patients. When IL-2 was an investigational agent, we were treating patients who, in retrospect, we probably shouldn't have treated. So, to be clear, it's not one out of 10 patients with kidney cancer overall who experience this benefit. Rather, it's 10 percent of a highly selected patient population.

Patients with clear cell carcinoma are candidates for IL-2. This approach does not work in papillary or collecting duct carcinoma. The ideal patient is younger than age 60, has a good performance status with no serious comorbid

conditions or coronary artery disease and has only soft tissue disease. We don't usually treat patients with IL-2 if they have extensive bone disease, but we do treat patients with lung or liver involvement.

DR LOVE: Is there any way to identify which patients will demonstrate response to IL-2?

DR REDMAN: Some data indicate that if the tumor is a high expresser of carbonic anhydrase-9 — meaning that more than 85 percent of the cells stain — it's more likely that the patient will benefit from high-dose IL-2, with response rates as high as 20 percent. This is an immunohistochemical stain, which is not standard. Also, some patients' tumors express less, but they still respond, so it's not an all-or-none phenomenon.

DR LOVE: What toxicities are associated with IL-2 treatment?

DR REDMAN: One cycle requires two five-day hospitalizations, and it is administered every eight hours. The patient is hospitalized because of the side effects and the medications required to control them. During administration, patients may experience nausea, vomiting, diarrhea, fluid retention, decreased renal output and hypotension that requires vasopressor support.

We treat the patients on a bone marrow transplant unit, and we do everything we can to control the side effects. Still, one out of every 10 patients becomes seriously ill. The full treatment consists of 14 doses, but it's unusual when treating patients with kidney cancer to administer all 14 doses. Treatment-related mortality occurs in less than one percent of patients, and it usually results from factors that we cannot prevent. A few patients will have diffuse cardiomyopathy from the IL-2, which we believe is autoimmune mediated.

DR LOVE: How long does it take for the patients to feel well again after the treatment?

DR REDMAN: They'll return to their baseline anytime from seven to 10 days after the IL-2 administration is complete. When they go home, their major symptoms are decreased appetite, fatigue and skin rash. They begin to feel better day by day, and about 10 days later, when they are feeling normal again, we bring them back for the second half of their treatment.

Track 11

DR LOVE: What is your view on the current role of bevacizumab in the treatment of RCC?

DR REDMAN: It hasn't been compared head to head with sunitinib, but I do believe bevacizumab has a role to play in the treatment of advanced kidney cancer. One trial evaluated interferon with or without bevacizumab, and the combination was superior (Rini 2008; [3.1]).

However, I believe interferon is no longer useful as a single agent. I stopped using it back in the 1990s. It's more toxic, without any benefit — consid-

ering the trial data, I hope no one is using it as monotherapy. I would have preferred a trial evaluating bevacizumab with or without interferon. I believe it's important to determine whether adding interferon improves the efficacy of bevacizumab enough to justify the additional toxicity.

DR LOVE: How are you using bevacizumab in practice?

DR REDMAN: We generally have a lot of clinical trials to offer patients. Outside of a trial, if a patient's disease responds to sunitinib and sorafenib and then progresses, I believe at that point it's valid to try bevacizumab or even temsirolimus.

DR LOVE: What's your experience with temsirolimus?

DR REDMAN: It's an FDA-approved therapy, and we use it off protocol. I haven't seen what I would call clinical responses, meaning tumor shrinkage — and it's difficult in a nonrandomized context to determine whether stable disease is secondary to the treatment or if it's a result of the nature of the kidney cancer itself. ■

3.1

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

Efficacy endpoints

	Bevacizumab + IFN (95% CI)	IFN (95% CI)	*p*-value
Median progression-free survival	8.5 months (7.5 to 9.7 months)	5.2 months (3.1 to 5.6 months)	<0.0001
Objective response rate	25.5% (20.9% to 30.6%)	13.1% (9.5% to 17.3%)	<0.0001

Select Grade III/IV toxicities

	Grade III		Grade IV	
	Bevacizumab + IFN	IFN	Bevacizumab + IFN	IFN
Anorexia	17%	8%	0%	0%
Fatigue	35%	28%	2%	2%
Hypertension	9%	0%	1%	0%
Proteinuria	13%	0%	2%	0%

CI = confidence interval

SOURCE: Rini BI et al. *J Clin Oncol* 2008;26(33):5422-8.

SELECT PUBLICATION

Rini BI et al. **Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206.** *J Clin Oncol* 2008;26(33):5422-8.

INTERVIEW

Roberto Pili, MD

Dr Pili is Professor of Oncology, Chief of the Genitourinary Section and Co-Leader of the Genitourinary Program at Roswell Park Cancer Institute in Buffalo, New York.

Tracks 1-10

Track 1	Investigating mechanisms of resistance to anti-VEGF agents
Track 2	Pathways being evaluated as targets in the treatment of RCC
Track 3	Predictors of response to targeted therapies for RCC
Track 4	**Case discussion:** A man in his midsixties who developed lymph node metastases one year after nephrectomy for clear cell RCC
Track 5	Treatment options for previously untreated mRCC
Track 6	Side effects associated with sunitinib
Track 7	Treatment options for patients with mRCC whose disease progresses on sunitinib
Track 8	Side-effect profile of axitinib in the treatment of mRCC
Track 9	Data evaluating bevacizumab for mRCC
Track 10	Key ongoing clinical trials in RCC

Select Excerpts from the Interview

Tracks 5, 9-10

DR LOVE: Which alternatives would you consider as first-line therapy for patients like yours, in their midsixties with relapsed, good-prognosis RCC?

DR PILI: We could consider different options, although the NCCN guidelines for a patient with newly diagnosed metastatic disease who has received no prior therapy, according to the Category 1 evidence, recommend sunitinib (Motzer 2007; Figlin 2008). Age in the midsixties probably does not make this patient the best candidate for high-dose IL-2. In general, we recommend that treatment for a younger patient with an excellent performance status and good lung and cardiac function.

DR LOVE: What about the use of bevacizumab alone or with interferon for patients whose disease progresses on sunitinib?

DR PILI: As you know, bevacizumab has been primarily developed in the first-line setting (4.1; [Melichar 2008]). Once bevacizumab is FDA approved for the treatment of kidney cancer, I believe it will be used in the first-line setting. If the interferon is dose reduced or discontinued, the toxicity profile may be better than that of sunitinib. So I believe it will play a role.

DR LOVE: Are any major randomized trials currently under way for metastatic RCC that oncologists in practice should know about?

DR PILI: The BeST trial (ECOG-E2804) is a relatively small Phase II randomized study. Different combinations of agents (bevacizumab/sorafenib, bevacizumab/temsirolimus or temsirolimus/sorafenib) are being compared to bevacizumab alone for metastatic RCC (4.2). ■

4.1

AVOREN: Subgroup Analysis of Reduced-Dose versus Full-Dose Interferon (IFN) in Combination with Bevacizumab (Bev) in Previously Untreated mRCC

Parameter	Reduced-dose IFN		Full-dose IFN		Total population	
	Bev + IFN (n = 124[a])	IFN + placebo (n = 90[a])	Bev + IFN (n = 174[a])	IFN + placebo (n = 186[a])	Bev + IFN (n = 298[a])	IFN + placebo (n = 276[a])
12-month PFS rate*	0.524		0.361		0.427	
Median duration of PFS*	HR = 0.63, $p = 0.0026$		HR = 0.69, $p = 0.0007$		HR = 0.63, $p < 0.0001$	
Overall response	34%	17% $p = 0.0181$	31%	12% $p < 0.0001$	32%	13% $p < 0.0001$
Median duration of response[b]	13.6mo	8.3mo	13.5mo	14.0mo	13.5mo	11.1mo

[a] Patients assessable; [b] Patients with measurable disease at baseline

* Values < 1.0 favor bevacizumab-containing regimens

"The results of the AVOREN trial have demonstrated that bevacizumab + IFN doubles the duration of median PFS compared with IFN + placebo in patients with mRCC. The present retrospective analysis of data from this trial indicates that in patients with mRCC receiving bevacizumab + IFN, the dose of IFN can be reduced to manage the side-effects of this agent while maintaining a significant efficacy benefit over IFN + placebo that is similar to that observed in patients who received full-dose IFN. . .

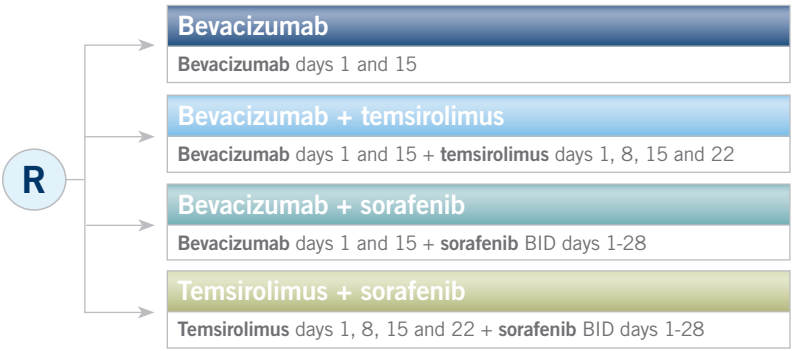
In the bevacizumab + IFN arm, the proportion of patients on reduced-dose IFN who were progression free at 12 months was greater than in those receiving full-dose IFN. A number of factors might have contributed to this. First, the duration of IFN treatment in those on a lower dose was longer. Second, a selection effect might have occurred, with responding patients being treated for long enough to develop symptoms requiring IFN dose reduction; notably, excluding those with early disease progression reduced the difference in the percentages of patients progression free at 12 months between the reduced- and full-dose subgroups (55% and 47%)."

SOURCE: Melichar B et al. *Ann Oncol* 2008;19(8):1470-6.

4.2

Phase II Randomized Trial of Bevacizumab, Sorafenib and Temsirolimus (BeST) for Patients with Metastatic Clear Cell RCC

Protocol ID: ECOG-E2804; Target Accrual: 360



Eligibility

- No history or clinical evidence of CNS disease, including primary brain tumor or brain metastases
- No history of bleeding diathesis or coagulopathy
- No clinically significant cardiovascular disease
- No serious, nonhealing wound, ulcer or bone fracture

Study Contact

Keith Flaherty, MD, Protocol Chair; Tel: 215-662-8624

SOURCE: NCI Physician Data Query, April 2009.

SELECT PUBLICATIONS

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* 2007;370(9605):2103-11.

Figlin RA et al. **Overall survival with sunitinib versus interferon (IFN)-alfa as first-line treatment of metastatic renal cell carcinoma (mRCC).** *Proc ASCO* 2008;**Abstract 5024**.

Melichar B et al. **First-line bevacizumab combined with reduced dose interferon-alpha2a is active in patients with metastatic renal cell carcinoma.** *Ann Oncol* 2008;19(8):1470-6.

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

National Comprehensive Cancer Network (NCCN®). **NCCN clinical practice guidelines in oncology, kidney cancer. Version 1. 2009**. Available at: **www.nccn.org/professionals/physician_gls/f_guidelines.asp**.

Rini BI et al. **Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206.** *J Clin Oncol* 2008a;26(33):5422-8.

Rini BI et al. **Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab-refractory metastatic renal cell carcinoma.** *J Clin Oncol* 2008b;26(22):3743-8.

Ryan CW et al; Southwest Oncology Group. **Sorafenib with interferon alfa-2b as first-line treatment of advanced renal carcinoma: A phase II study of the Southwest Oncology Group.** *J Clin Oncol* 2007;25(22):3296-301.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The randomized adjuvant Phase III ECOG-E2805 trial is evaluating _____ versus _____ for patients with resected RCC.**
   a. Bevacizumab; interferon
   b. Bevacizumab; erlotinib
   c. Sunitinib; sorafenib
   d. Axitinib; sorafenib
2. **A Phase II trial of pazopanib for patients with mRCC reported a correlation between circulating VEGFR2 levels and patient response.**
   a. True
   b. False
3. **A Phase III trial revealed a significant improvement in progression-free survival with everolimus compared to placebo for patients with mRCC progressing on sunitinib or sorafenib.**
   a. True
   b. False
4. **Which of the following trials has evaluated bevacizumab in combination with interferon for patients with mRCC?**
   a. AVOREN
   b. CALGB-90206
   c. ARCCS
   d. Both a and b
   e. All of the above
5. **In a Phase II, randomized discontinuation trial of _____, a second-generation tyrosine kinase inhibitor, the randomization was terminated early to prevent discontinuation of the drug for patients who were experiencing benefit.**
   a. Sunitinib
   b. Pazopanib
   c. Axitinib
   d. Both b and c
   e. None of the above
6. **High-dose interleukin-2 (IL-2) is effective in the treatment of which subtype of RCC?**
   a. Clear cell
   b. Collecting duct
   c. Papillary
   d. All of the above
7. **Data indicate that patients whose tumors are high expressers of carbonic anhydrase-9 are _____ to benefit from high-dose IL-2.**
   a. More likely
   b. Less likely
8. **In a Phase III trial of interferon with or without bevacizumab for patients with previously untreated mRCC, which of the following efficacy endpoints was significantly higher among the patients who received both agents?**
   a. Median progression-free survival
   b. Objective response rate
   c. Both a and b
   d. None of the above
9. **According to the NCCN guidelines for kidney cancer (Version 1. 2009), which of the following agents is supported by Category I (randomized trial) evidence as first-line therapy for relapsed or mRCC?**
   a. Sunitinib
   b. Sorafenib
   c. Bevacizumab with interferon
   d. Both a and b
   e. Both a and c
10. **In a subset analysis of the AVOREN trial, patients who received reduced doses of interferon in combination with bevacizumab had _____ efficacy outcomes compared to those who received full doses of interferon in combination with bevacizumab.**
    a. Better
    b. Worse
    c. Similar
11. **The BeST trial (ECOG-E2804) will evaluate single-agent bevacizumab versus which of the following combination therapies?**
    a. Temsirolimus/bevacizumab
    b. Sorafenib/bevacizumab
    c. Temsirolimus/sorafenib
    d. All of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Renal Cell Cancer Update — Issue 1, 2009

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 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

- ECOG-E2805: Adjuvant trial of sunitinib versus sorafenib versus placebo for resected RCC 4 3 2 1
- Efficacy and tolerability of sorafenib for older patients with advanced RCC 4 3 2 1
- Clinical trial data with pazopanib or axitinib in RCC 4 3 2 1
- Impact of interferon dose reductions on the clinical benefit of bevacizumab/interferon in the AVOREN trial 4 3 2 1
- Benefits and risks associated with high-dose interleukin-2 (IL-2) for advanced RCC 4 3 2 1
- Clinical use of bevacizumab with or without interferon 4 3 2 1

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

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

- ECOG-E2805: Adjuvant trial of sunitinib versus sorafenib versus placebo for resected RCC 4 3 2 1
- Efficacy and tolerability of sorafenib for older patients with advanced RCC 4 3 2 1
- Clinical trial data with pazopanib or axitinib in RCC 4 3 2 1
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- Benefits and risks associated with high-dose interleukin-2 (IL-2) for advanced RCC 4 3 2 1
- Clinical use of bevacizumab with or without interferon 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 be able to:

- Use prognostic tools to estimate risk of disease recurrence, and communicate these findings to patients with resected renal cell cancer (RCC) ..... 4 3 2 1 N/M N/A
- Demonstrate an understanding of the biology of clear cell RCC, including inactivation of the von Hippel-Lindau (VHL) tumor-suppressor gene and the pathway leading to VEGF overexpression ..... 4 3 2 1 N/M N/A
- Develop an approach for the sequencing of therapies for advanced RCC, incorporating biologic response modifiers, tyrosine kinase inhibitors (TKIs), anti-VEGF antibodies and mTOR inhibitors ..... 4 3 2 1 N/M N/A
- Inform patients about the side effects associated with various therapeutic options when recommending systemic treatment for advanced RCC ..... 4 3 2 1 N/M N/A
- Critically evaluate emerging clinical trial data with second-generation TKIs, and appraise their impact on the RCC treatment algorithm ..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with RCC about participation in ongoing 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?

.....

.....

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

.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ☐ Yes, I am willing to participate in a follow-up survey.
- ☐ No, I am not willing to participate in a follow-up survey.

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4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Robert A Figlin, MD	4 3 2 1	4 3 2 1
Ronald M Bukowski, MD	4 3 2 1	4 3 2 1
Bruce G Redman, DO	4 3 2 1	4 3 2 1
Roberto Pili, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the editor and faculty for this activity:

.....

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Renal Cell Cancer™

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