Second in a Three-Part Series

Renal Cell Cancer™

U P D A T E

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

INTERVIEWS

Thomas E Hutson, DO, PharmD
Walter Stadler, MD
Brian I Rini, MD
Nicholas J Vogelzang, MD

With Comments on a National Patterns of Care Study of Medical Oncologists

Also visit ResearchToPractice.com/RCCUSEvideo09 for related faculty videos

Cosponsored by Research To Practice and City of Hope.

CME Certified

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 multiple 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 to provide access to the latest research developments. Through critical review of the evidence and expert perspectives, this CME activity assists medical oncologists with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Identify patient characteristics that may help to distinguish the individualized utility of cytoreductive nephrectomy in the era of effective targeted therapies for metastatic renal cell carcinoma (mRCC).
- Summarize the feasibility and safety of nephrectomy after preoperative use of targeted systemic treatments for RCC.
- Apply the results of existing and emerging clinical research to incorporate multitargeted tyrosine kinase inhibitors, monoclonal antibodies, mTOR inhibitors and cytokines in the management of advanced RCC.
- Educate patients with advanced RCC about side effects associated with available systemic treatment options.
- Recommend supportive measures to enhance the tolerability of targeted therapeutic agents for RCC, including the judicious use of dose reductions and schedule changes.
- Critically evaluate emerging clinical trial data with the second-generation tyrosine kinase inhibitors, and assess how these agents may modify existing RCC treatment algorithms.
- Counsel appropriately selected patients with RCC about participation in ongoing clinical trials in the adjuvant and metastatic settings.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

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

HOW TO USE THIS CME ACTIVITY

This CME activity contains both audio and print components. To receive credit, the participant should review the CME information, listen to the CDs, review the monograph and complete the Post-test and Educational Assessment and Credit Form located in the back of this monograph or on our website at **CME.ResearchToPractice.com**. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ResearchToPractice.com/RCCUSE09** includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated within the text of the monograph in **blue, bold text**.

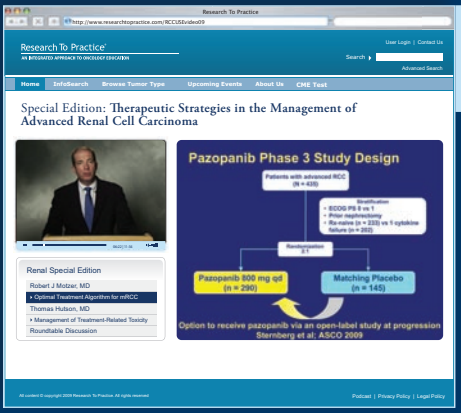
This program is supported by an educational grant from GlaxoSmithKline.

Last review date: December 2009; Release date: December 2009; Expiration date: December 2010

TABLE OF CONTENTS

INTERVIEWS

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantor.



Video roundtable discussion and slide presentations by Drs Hutson and Motzer

Visit ResearchToPractice.com/RCCUSEvideo09 to view video slide presentations by Dr Thomas Hutson and Dr Robert Motzer and an engaging roundtable discussion with both oncologists on the management of side effects of newer biologic agents in renal cell cancer.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — 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 Hutson** — Advisory Committee: Bayer Pharmaceuticals Corporation, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth; Consulting Agreements: Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth; Paid Research: GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth; Speakers Bureau: Bayer Pharmaceuticals Corporation, Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth. **Dr Stadler** — Advisory Committee: Bayer Pharmaceuticals Corporation, Wyeth; Consulting Agreements: AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation, Genentech BioOncology, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc; Stock Ownership: Abbott Laboratories. **Dr Rini** — Advisory Committee: Bayer Pharmaceuticals Corporation, Genentech BioOncology, Genomic Health Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth; Paid Research: Pfizer Inc. **Dr Vogelzang** — Consulting Agreements and Speakers Bureau: Abbott Laboratories, Allos Therapeutics, Amgen Inc, Argos Therapeutics Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation, Bristol-Myers Squibb Company, Centocor Ortho Biotech Services LLC, Cougar Biotechnology Inc, Dendreon, EMD Serono Inc, Genentech BioOncology, Genta Inc, GlaxoSmithKline, GPC Biotech, Keryx Biopharmaceuticals Inc, Lilly USA LLC, Merck and Company Inc, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Pfizer Inc, Sanofi-Aventis, Wyeth; Research Support: Abbott Laboratories, Alfacell Corporation, ArQule, Astellas US LLC, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation, CanBas Co Ltd, Dendreon, Lilly USA LLC, Medarex Inc, Merck and Company Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi-Aventis, WILEX AG.

EDITOR — **Neil Love:** Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Centocor Ortho Biotech Services LLC, Cephalon Inc, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Genzyme Corporation, GlaxoSmithKline, ImClone Systems Incorporated, Lilly USA LLC, Merck and Company Inc, Millennium Pharmaceuticals Inc, Monogram Biosciences, Novartis Pharmaceuticals Corporation, OSI Oncology, Roche Laboratories Inc, Sanofi-Aventis and Wyeth.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

INTERVIEW

Thomas E Hutson, DO, PharmD

Dr Hutson is Director of the GU Oncology Program at Texas Oncology-Baylor Charles A Sammons Cancer Center and Co-Chair of US Oncology GU Research in Dallas, Texas.

Tracks 1-18

Select Excerpts from the Interview

Track 3

DR LOVE: Is cytoreductive nephrectomy always indicated for patients who present with metastatic renal cell cancer and an intact primary tumor?

DR HUTSON: That's probably one of the most important questions in the treatment of kidney cancer right now. As oncologists, we are not used to conducting cytoreductive surgery for patients with metastatic disease. It's the concept of "first, do no harm." However, with kidney cancer we have data that support cytoreductive surgery.

In the 1990s, a multivariate analysis of large data sets showed that patients who underwent cytoreductive nephrectomy seemed to fare better and live longer. That prompted two small trials that randomly assigned patients with metastatic renal cell carcinoma (mRCC) to interferon with or without nephrectomy.

Both trials demonstrated a survival benefit with nephrectomy (Flanigan 2001; Mickisch 2001). Also, it was noted that cytokine therapy did not reduce the size of the primary tumor.

Today, with more active therapy, we see responses in the primary tumor, which raises the question whether cytoreductive nephrectomy provides a meaningful improvement in survival in this setting.

To address this, the French launched the CARMENA trial, which randomly assigns patients to sunitinib alone or cytoreductive nephrectomy followed by sunitinib. Discussion of conducting an Intergroup trial with a similar design has also taken place among the cooperative groups.

DR LOVE: How do you approach this issue in practice?

DR HUTSON: I believe cytoreductive nephrectomy should be considered for such patients but performed only in select cases. If the majority of the total cancer volume can be removed, performance status is acceptable and no comorbidities are present, then cytoreductive nephrectomy should be performed.

Reports from some institutions have tried to determine what proportion of tumor should be removable to consider surgery. Some believe that if 80 to 85 percent of the total cancer volume can be removed, then the patient should undergo nephrectomy.

Track 8

DR LOVE: How do you manage the toxicities associated with multitargeted tyrosine kinase inhibitors (TKIs)?

DR HUTSON: First, we discuss with the patient expectations of treatment and potential toxicities, focusing on a balance between quality of life and what patients can expect to gain from the medication.

It's also important to explain to a patient that "more is better" with these agents. When we perform pharmacokinetic analyses with the multitargeted TKIs, we're able to show that more drug exposure, as measured by the area under the curve, is associated with a higher efficacy. Therefore, the physician should always try to maintain dose intensity as long as possible. When

my patients experience toxicities, we discuss their side effects and the data that demonstrate that reducing the dose of therapy may be less efficacious.

If patients' quality of life is suffering, then one needs to intervene, but before reducing the dose, we try a variety of supportive measures, such as pedicures and changing the types of shoes they wear for hand-foot syndrome, topical agents for mucositis or pharmaceutical agents for heartburn.

If it reaches the point that, despite these maneuvers, the toxicities are still adversely affecting quality of life, then we move to dose interruption for two or three days. The toxicity usually resolves or improves significantly during that break, and then we resume therapy at a lower dose.

Track 9

DR LOVE: What is the most common side effect you see with sunitinib?

DR HUTSON: Fatigue. In the pivotal clinical trial comparing sunitinib to interferon, the degree of fatigue was similar between the two agents, occurring in more than 50 percent of the patients (Motzer 2007).

If a patient is experiencing Grade III fatigue, there should be interruption or reduction of treatment. Sunitinib can induce hypothyroidism, so we also need to check for that and treat with levothyroxine if indicated. We don't understand the cause of fatigue above and beyond that. Some physicians prescribe stimulants, such as methylphenidate. Steroids should be avoided because they increase the metabolism of sunitinib.

My approach is to reduce sunitinib from the standard dose of 50 milligrams to 37.5 milligrams, keeping the patient on a four-weeks-on, two-weeks-off schedule (1.1).

1.1

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."

[Citations omitted]

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

Tracks 11-12

DR LOVE: Outside of a trial, how do you sequence the available systemic therapies?

DR HUTSON: In treating mRCC, the goal is to provide patients with all of the known active drugs at some point in their treatment course. However, we don't know the appropriate sequence of these agents. Sunitinib is the most potent available drug, and patients with good- and intermediate-risk disease should receive it up front. Patients with poor-risk disease should receive temsirolimus. Upon disease progression, it becomes less clear.

In practice, I discuss second-line options with my patients and I lean toward an mTOR inhibitor, either temsirolimus or everolimus. Phase III data support everolimus in the refractory second line and beyond, with an updated progression-free survival of approximately five months (Kay 2009).

Tracks 14-15

DR LOVE: Would you summarize what we know about the second-generation TKIs axitinib and pazopanib?

DR HUTSON: We currently have multiple agents that provide benefit but with toxicities.

One goal is to find newer agents that are either more potent or less toxic and are more amenable to long-term use. Both axitinib and pazopanib appear to be more tolerable than sunitinib and sorafenib in that we see significantly fewer instances of diarrhea, fatigue, hand-foot syndrome and mucositis.

Most of the efficacy data exist with pazopanib. In a Phase II trial evaluating pazopanib for patients who had either received previous cytokine therapy or had treatment-naïve disease, the objective response rate was around 30 percent and progression-free survival was approximately 11 months (Hutson 2008a). The efficacy data were similar to those with sunitinib, but significantly fewer cases of hand-foot syndrome and fatigue were observed.

At ASCO 2009 results from a Phase III trial comparing pazopanib to placebo were presented (Sternberg 2009; [1.2]), and they were similar to the Phase II data. Again, the progression-free survival rate was similar to that of sunitinib but with a different toxicity profile.

Currently, a global Phase III trial is comparing sunitinib to pazopanib as front-line therapy. It is open at many sites in the United States and is rapidly accruing. Also, investigators at Memorial Sloan-Kettering are comparing second-line axitinib to sorafenib in the Phase III AXIS trial.

I believe that the second-generation TKIs, axitinib and pazopanib, hold promise. If pazopanib were available today and had an approval indication as initial therapy, I would be using it for most of my patients up front. (*Editor's*

note: On October 19, 2009, after this interview was conducted, the FDA approved pazopanib for the treatment of advanced RCC.) ■

1.2

Phase III Trial of Pazopanib versus Placebo for Patients with Treatment-Naïve and Cytokine-Pretreated Advanced RCC

Overall efficacy data

	Pazopanib (n = 290)	Placebo (n = 145)	Hazard ratio
Median progression-free survival (PFS)	9.2 mo	4.2 mo	0.46[1]
Median overall survival (OS)	21.1 mo	18.7 mo*	0.73[2]
Overall response rate (ORR, CR + PR)	30%	3%	—
Duration of response (DoR)	59 wk	—	—

[1] $p < 0.0000001$; [2] $p < 0.02$
* 48% of patients received pazopanib after disease progression.

Toxicity data

All grades	Pazopanib (n = 290)	Placebo (n = 145)
Hypothyroidism	7%	0%
Hand-foot syndrome	6%	<1%
Mucositis/stomatitis	4%/4%	<1%/0%
Arterial thromboembolism (≥Grade III)	3% (2%)	0%

SOURCE: Sternberg CN et al. *Proc ASCO* 2009;**Abstract 5021**.

SELECT PUBLICATIONS

Flanigan RC et al. **Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer.** *N Engl J Med* 2001;345(23):1655-9.

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.

Kay A et al. **Updated data from a phase III randomized trial of everolimus (RAD001) versus PBO in metastatic renal cell carcinoma (mRCC).** *Proc Genitourinary Cancers Symposium* 2009;**Abstract 278**.

Mickisch GH et al. **Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: A randomised trial.** *Lancet* 2001;358(9286):966-70.

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

Sternberg CN et al. **A randomized, double-blind phase III study of pazopanib in treatment-naïve and cytokine-pretreated patients with advanced renal cell carcinoma (RCC).** *Proc ASCO* 2009;**Abstract 5021**.

INTERVIEW

Walter Stadler, MD

Dr Stadler is Fred C Buffet Professor and Associate Dean of Clinical Research in the Departments of Medicine and Surgery, Sections of Hematology/Oncology and Urology and is Director of Genitourinary Oncology at the University of Chicago in Chicago, Illinois.

Tracks 1-8

Select Excerpts from the Interview

Track 2

DR LOVE: How has the FDA approval of bevacizumab/interferon for mRCC influenced your selection of first-line therapy?

DR STADLER: The trials that led to that FDA approval of bevacizumab evaluated the combination of bevacizumab/interferon (Escudier 2007; Rini 2008; [2.1]). Few data in the first-line setting are available to determine whether bevacizumab monotherapy is as efficacious. Therefore, if bevacizumab is used in the first-line setting, it should be in combination with interferon.

DR LOVE: How do you usually select first-line therapy outside of a protocol?

DR STADLER: For patients with good-prognosis disease, sunitinib remains as standard first-line therapy. Sorafenib and the combination of bevacizumab/interferon are also alternatives.

For a younger individual with a good cardiorespiratory status, one could consider high-dose interleukin-2 (IL-2). For a patient with poor-prognosis disease, the data suggest that temsirolimus should be first-line therapy.

2.1

Phase III Randomized Trials Comparing Bevacizumab/Interferon to Interferon for Previously Untreated mRCC

	AVOREN[1]		CALGB-90206[2]	
	Bevacizumab + interferon (n = 327)	Placebo + interferon (n = 322)	Bevacizumab + interferon (n = 369)	Interferon (n = 363)
Median PFS	10.2 months*	5.4 months	8.5 months†	5.2 months

* $p = 0.0001$; † $p < 0.0001$; PFS = progression-free survival

SOURCES: [1] Escudier B et al; AVOREN Trial Investigators. *Lancet* 2007;370(9605):2103-11; [2] Rini BI et al. *J Clin Oncol* 2008;26(33):5422-8.

Track 4

DR LOVE: Would you discuss the second-generation multitargeted TKI pazopanib?

DR STADLER: An important Phase III trial comparing pazopanib to placebo was presented at ASCO. Patients with mRCC treated with pazopanib showed a dramatic improvement in time to disease progression compared to placebo (Sternberg 2009; [1.2, page 7]).

From an efficacy standpoint, pazopanib appears similar to sunitinib. From a toxicity standpoint, it yields fewer skin and gastrointestinal toxicities.

Somewhat more liver toxicity may be present with pazopanib than was seen with sunitinib, comparing across trials rather than directly. A larger comparative trial of sunitinib versus pazopanib is under way, and we'll see whether those impressions hold up.

Tracks 6-7

DR LOVE: In which clinical situations would you use an mTOR inhibitor as opposed to sunitinib as first-line therapy?

DR STADLER: For patients with overall poor prognoses according to the Memorial Sloan-Kettering criteria (Motzer 2002; [2.2]), I would consider temsirolimus or another mTOR inhibitor up front.

Temsirolimus is indicated for first-line therapy for patients with poor-prognosis disease, and everolimus is for patients who have previously received a multitargeted TKI. I would consider both agents modestly effective and more similar than different. Temsirolimus is administered intravenously, and everolimus is taken orally.

They have similar toxicity profiles with regard to hyperglycemia, hypercholesterolemia, edema, stomatitis and occasional pneumonitis.

DR LOVE: Would you discuss the specific side effects associated with the mTOR inhibitors?

DR STADLER: Metabolic problems are common. Almost everyone receiving these agents develops some elevation in serum glucose or cholesterol.

Patients with baseline diabetes are often problematic. It can turn a disease that doesn't need treatment into one that does because the serum glucose is elevated enough to cause significant problems.

The lipids become less of a problem clinically in a setting in which patients may have a limited lifespan. However, we occasionally see elevations in triglycerides to levels at which we're theoretically concerned about pancreatitis.

mTOR inhibitors are also associated with an allergic interstitial pneumonitis that is sometimes clinically difficult to distinguish from infection or progressive disease in patients with disease in the lungs. It is similar to other drug-induced allergic pneumonitis and responds well to steroids.

The classic mTOR inhibitor to which all these drugs are related is sirolimus, an immunosuppressive agent used for patients with kidney transplants. All of the mTOR inhibitors are potent lymphotoxins. So we also see an increased risk of infections, specifically in the lungs. ■

2.2

Memorial Sloan-Kettering Criteria for Prognosis of RCC

Risk factors for short survival

- Karnofsky performance status: <80%
- LDH: >1.5 times upper limit of normal
- Hemoglobin: <lower limit of normal
- Corrected serum calcium: >10 mg/dL
- Time from initial diagnosis to treatment with interferon: <1 year

Risk group	Number of risk factors
Poor risk	≥3 risk factors
Intermediate risk	1 to 2 risk factors
Favorable risk	0 risk factors

SOURCE: Motzer RJ et al. *J Clin Oncol* 2002;20(1):289-96.

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.

Motzer RJ et al. **Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma.** *J Clin Oncol* 1999;17(8):2530-40.

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.

Sternberg CN et al. **A randomized, double-blind phase III study of pazopanib in treatment-naïve and cytokine-pretreated patients with advanced renal cell carcinoma (RCC).** *Proc ASCO* 2009;**Abstract 5021**.

INTERVIEW

Brian I Rini, MD

Dr Rini is Associate Professor of Medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University in Cleveland, Ohio.

Tracks 1-16

Select Excerpts from the Interview

Track 3

DR LOVE: Would you discuss your recent paper on surgical resection of RCC after treatment with targeted therapy?

DR RINI: It was a retrospective study including 19 patients with initially unresectable primary RCC who had great responses to systemic therapy,

primarily sunitinib. Then 12 to 24 months later we questioned whether we could remove the bulk of the patient's disease (Thomas 2009).

The data demonstrated that patients can safely undergo surgery after targeted therapy (Thomas 2009). We shouldn't forget that the curative therapy for kidney cancer, metastatic or otherwise, is surgery. If patients are at a point at which their treatment can be consolidated with surgery, it needs to be considered in your regimen.

DR LOVE: What did you see in terms of anti-VEGF-related complications?

DR RINI: We didn't have the impression that the patients experienced any more surgical complications than we would have expected (Thomas 2009). In terms of wound-healing complications, we know that the half-lives for the TKIs are much shorter than that of bevacizumab because they're small molecules. Our general practice is to keep patients off of therapy for seven days before surgery.

Track 4

DR LOVE: You were an author on an abstract presented at ASCO 2009 on the association between the proportion of tumor burden removed with debulking nephrectomy and progression-free survival. What did you see?

DR RINI: It was our attempt to retrospectively evaluate the practice of debulking nephrectomy in the modern era of targeted therapy, largely sunitinib. We found, not surprisingly, that patients who have a larger proportion of their total tumor burden removed at the time of nephrectomy fare better (Barbastefano 2009).

A patient with a large primary tumor and a small burden of metastatic disease can expect to fare better than a patient with a 3-cm primary tumor and a total of 15 centimeters of disease elsewhere. To me, that makes intuitive, clinical common sense, but we wanted to examine it along with other factors that might be important. It doesn't prove that debulking nephrectomy is beneficial in the era of targeted therapy, but to me it says that if you undertake that approach, patient selection is still vital.

Track 6

DR LOVE: What has been your experience when counseling patients about the adjuvant trial ECOG-E2805, evaluating sunitinib versus sorafenib versus placebo (3.1)?

DR RINI: When I'm meeting with a patient who has undergone surgery and does not have obvious metastatic disease, I usually ask two questions. First, what is the risk of recurrence? Basing it primarily on stage and grade, I provide my estimate of the risk of recurrence.

Second, what will reduce that risk? The short answer is that absolutely nothing has ever been proven to reduce that risk. Then I'll launch into a discussion about the clinical trials, saying, "We now have these new drugs in the advanced disease setting that we are starting to study in earlier disease, but they may or may not reduce the risk of recurrence."

Although we offer participation in ECOG-E2805 to any eligible patient, I believe that my enthusiasm is more for the younger patient with T3 and/or node-positive disease than for the patient with a 6-cm renal mass who might be on the fringe of being eligible from a risk perspective. Again, we realize that side effects can occur with these agents that may be life altering, especially for patients who are not experiencing symptoms.

3.1

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

Protocol IDs: ECOG-E2805, CALGB-E2805, SWOG-E2805, CAN-NCIC-E2805, NCT00326898

Target Accrual: 1,923
Current Accrual: 1,461 (9/12/09)
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

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

Track 11

DR LOVE: In our Patterns of Care survey, we presented a 57-year-old patient with a resected, pT3aN0M0, Grade III, clear cell carcinoma, and the initial treatment preferred by 29 percent of the community-based oncologists was sunitinib. Any thoughts?

DR RINI: I haven't administered sunitinib to a patient off study in the adjuvant setting. Not a single study exists that would suggest any benefit. Having administered the drug to enough people, I realize that significant toxicity can occur. We also don't know what effect adjuvant sunitinib might

have on the biology of response in the metastatic setting if the patient's disease recurs.

Sometimes I'll see patients who want adjuvant therapy, but once I explain the risks versus benefit, I've never had a patient challenge me. I explain that the benefit is unproven and that we would be exposing the patient to risk.

Track 13

DR LOVE: How do you see investigators and oncologists in practice responding to the recent approval of bevacizumab/interferon? It seems a bit muted.

DR RINI: I believe that the diminished enthusiasm has to do with interferon being part of the regimen. Oncologists in the United States have never been excited about using interferon for kidney cancer.

I believe it also has to do with timing. Had these been the first data reported, it would have been more exciting. Three or four drugs, however, were FDA approved first and had their own exciting data. I believe being the fifth regimen diminished the excitement level.

Bevacizumab monotherapy has data to support its use in kidney cancer (Yang 2003), although it's not the highest level of evidence. It would, however, be well tolerated as monotherapy.

We need to figure out several issues during the next year or two: How do we incorporate this regimen? How much interferon is needed? Can we simply use interferon for some period of time and then use bevacizumab monotherapy? Based on the risk-to-benefit ratio, is it best as initial therapy for some patients or subsequent therapy for others? ■

SELECT PUBLICATIONS

Barbastefano J. **Association of percentage of tumor burden removed with debulking nephrectomy and progression-free survival (PFS) in metastatic renal cell carcinoma (mRCC) patients (Pts) treated with VEGF-targeted therapy.** *Proc ASCO* 2009;**Abstract 5095**.

Clark JI et al. **Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: A Cytokine Working Group randomized trial.** *J Clin Oncol* 2003;21(16):3133-40.

Escudier B et al. **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.

Rini B 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.

Thomas AA et al. **Surgical resection of renal cell carcinoma after targeted therapy.** *J Urol* 2009;182(3):881-6.

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

Nicholas J Vogelzang, MD

Dr Vogelzang is Chair and Medical Director of the Developmental Therapeutics Committee and Co-Chair of the GU Committee for US Oncology Research via Comprehensive Cancer Centers of Nevada in Las Vegas, Nevada.

Tracks 1-15

Select Excerpts from the Interview

Track 1

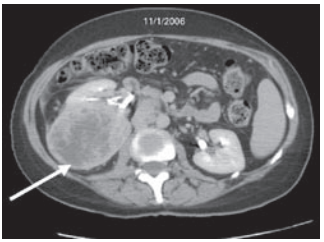
DR LOVE: Would you comment on your recent case report that was published in the *Journal of Clinical Oncology* of the woman with an intact primary RCC and widespread mRCC whom you have treated for 28 months with sequential anti-angiogenic therapy (Vogelzang 2009; [4.1])?

DR VOGELZANG: This 49-year-old woman presented with a small, clear cell RCC with widespread metastatic disease. Removing the primary tumor would likely confer no major benefit to her, and we believed that we could treat the primary tumor with sunitinib. Increasingly, we are seeing this scenario in practice. With long-term follow-up, we observe that many of the primary tumors regress to a great extent when treated with anti-angiogenic therapy. I

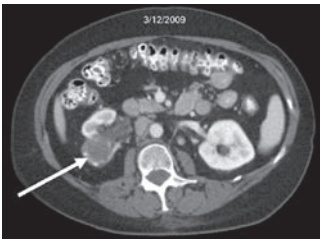
now have numerous patients for whom I simply watched the primary tumor and treated the metastatic disease, which was symptomatic and more life threatening. This patient also had a pathologic fracture that still needed to be treated. So at this point the primary tumor became a nonissue in my opinion. Of note, many oncologists are still focusing on the primary lesion despite increasing anecdotal experiences and an emerging body of literature suggesting that the urgency to remove the primary tumor has diminished considerably.

4.1

Long-Term Response in Primary Renal Cancer to Sequential Anti-Angiogenic Therapy



Primary renal mass (arrow) in November 2006 before the initiation of anti-angiogenic therapy.



Primary renal mass in March 2009 after more than 29 months of anti-angiogenic therapy. Note that ectopic calcification has developed in the mass (arrow).

SOURCE: With permission from Vogelzang NJ et al. *J Clin Oncol* 2009;27(26):e106-7.

Track 8

DR LOVE: How do you see bevacizumab alone or with interferon comparing to sunitinib or sorafenib in first-line treatment of mRCC?

DR VOGELZANG: The evidence supporting sunitinib for metastatic disease is overwhelming. When compared to interferon as front-line therapy, the sunitinib arm reached a median survival of 26 months (Motzer 2009).

In nondirect comparisons, bevacizumab/interferon is better than sorafenib, and it doesn't appear to be inferior to sunitinib. In the CALGB-90206 trial, the combination resulted in a progression-free survival of around nine months, and in the AVOREN trial it reached 10 or 11 months for the patients at good risk (Rini 2008; Escudier 2007; [2.1, page 9]). It may be that bevacizumab/interferon preserves sensitivity to sunitinib. In the AVOREN data, patients who initially received bevacizumab/interferon and then second- or third-line sunitinib had excellent median survival and progression-free survival rates (Escudier 2007).

I believe that it probably doesn't matter whether patients receive bevacizumab/interferon or sunitinib first, as long as they receive all of the active drugs at some point.

Track 9

DR LOVE: How do you think pazopanib will end up comparing to sunitinib as front-line therapy?

DR VOGELZANG: Based on a Phase III trial comparing pazopanib to placebo for patients with advanced RCC who were treatment-naïve or pretreated with cytokine therapy, it appears that pazopanib is as good as sunitinib with regard to progression-free survival, with perhaps a slightly lower overall response rate (Sternberg 2009; [1.2, page 7]).

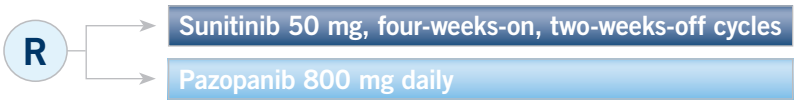
As for tolerability, I've heard people say that they believe that pazopanib is significantly less toxic than sunitinib through indirect comparisons. Data from the Phase III trial showed that pazopanib may cause more hepatic toxicity and bone marrow suppression, but we don't know because we haven't seen the full publication. We don't have head-to-head data, but a Phase III study is directly comparing front-line pazopanib to sunitinib (4.2). ■

4.2

Phase III Trial Comparing Pazopanib to Sunitinib

Protocol IDs: COMPARZ, 108844, NCT00720941
Target Accrual: 876 (Open)

Study Contact
GSK Clinical Trials Call Center
Tel: 877-379-3718



Eligibility

- Previously untreated, locally advanced and/or metastatic RCC

SOURCES: NCI Physician Data Query, October 2009; **www.clinicaltrials.gov**, October 2009.

SELECT PUBLICATIONS

Escudier B et al. **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.

Motzer RJ et al. **Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma.** *J Clin Oncol* 2009;27(22):3584-90.

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.

Sternberg CN et al. **A randomized, double-blind phase III study of pazopanib in treatment-naïve and cytokine-pretreated patients with advanced renal cell carcinoma (RCC).** *Proc ASCO* 2009;**Abstract 5021**.

Vogelzang NJ et al. **Long-term response in primary renal cancer to sequential antiangiogenic therapy.** *J Clin Oncol* 2009;27(26):e106-7.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **To evaluate the role of cytoreductive nephrectomy for patients who present with metastatic renal cell carcinoma, the CARMENA trial randomly assigns patients to _____ alone or after nephrectomy.**
   a. Sorafenib
   b. Sunitinib
   c. Temsirolimus

2. **The recommended standard starting dose for sunitinib for patients with advanced RCC is _____ daily, with or without food, on a four-weeks-on, two-weeks-off schedule.**
   a. 25 milligrams
   b. 37.5 milligrams
   c. 50 milligrams

3. **Which of the mTOR inhibitors is administered orally?**
   a. Everolimus
   b. Temsirolimus
   c. Both a and b

4. **In a Phase III trial comparing pazopanib to placebo in advanced renal cell carcinoma, median progression-free survival for patients who received pazopanib was _____ compared to 4.2 months for patients on the placebo arm.**
   a. 5.6 months
   b. 6.2 months
   c. 7.3 months
   d. 9.2 months

5. **Bevacizumab was FDA approved for mRCC based on clinical trials evaluating it in combination with _____.**
   a. Sunitinib
   b. Sorafenib
   c. Interferon
   d. Interleukin

6. **Which of the following metabolic abnormalities may be associated with the mTOR inhibitors?**
   a. Hyperglycemia
   b. Hypercholesterolemia
   c. Hypertriglyceridemia
   d. All of the above

7. **ECOG-E2805 is a Phase III, randomized, placebo-controlled adjuvant trial evaluating _____ versus _____ for patients with resected RCC.**
   a. Bevacizumab; interferon
   b. Bevacizumab; erlotinib
   c. Sunitinib; sorafenib
   d. Axitinib; sorafenib

8. **A Phase III trial is being conducted comparing pazopanib to _____ as front-line therapy for locally advanced and/or metastatic RCC.**
   a. Bevacizumab
   b. Bevacizumab/interferon
   c. Sorafenib
   d. Sunitinib

9. **In clinical trials evaluating continuous once-daily dosing of sunitinib, the dose used is _____.**
   a. 50 milligrams
   b. 37.5 milligrams
   c. 25 milligrams

10. **Which of the following is a commonly observed side effect with sunitinib in the treatment of advanced renal cell carcinoma?**
    a. Noninfection pneumonitis
    b. Metabolic syndrome
    c. Fatigue

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Renal Cell Cancer Update Special Edition — 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

How would you characterize your level of knowledge on the following topics?

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

	BEFORE	AFTER
Awareness of the ECOG-E2805 (ASSURE) ongoing clinical trial: Adjuvant sunitinib, sorafenib or placebo in unfavorable-risk RCC	4 3 2 1	4 3 2 1
Efficacy and safety of pazopanib in patients with advanced, treatment-naïve and cytokine-pretreated RCC	4 3 2 1	4 3 2 1
Bevacizumab with or without interferon in the treatment of mRCC	4 3 2 1	4 3 2 1
Fatigue as a treatment-limiting side effect of sunitinib	4 3 2 1	4 3 2 1
mTOR inhibitor-associated pneumonitis and cytopenias	4 3 2 1	4 3 2 1
Perspectives on the role of nephrectomy for patients with asymptomatic primary RCC and mRCC	4 3 2 1	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 learning objectives (LOs) by circling the appropriate selection:

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

As a result of this activity, I will be able to:

- Identify patient characteristics that may help to distinguish the individualized utility of cytoreductive nephrectomy in the era of effective targeted therapies for metastatic renal cell carcinoma (mRCC). . . . . 4 3 2 1 N/M N/A
- Summarize the feasibility and safety of nephrectomy after preoperative use of targeted systemic treatments for RCC. . . . . 4 3 2 1 N/M N/A
- Apply the results of existing and emerging clinical research to incorporate multitargeted tyrosine kinase inhibitors, monoclonal antibodies, mTOR inhibitors and cytokines in the management of advanced RCC. . . . . 4 3 2 1 N/M N/A
- Educate patients with advanced RCC about side effects associated with available systemic treatment options.. . . . . 4 3 2 1 N/M N/A
- Recommend supportive measures to enhance the tolerability of targeted therapeutic agents for RCC, including the judicious use of dose reductions and schedule changes. . . . . 4 3 2 1 N/M N/A
- Critically evaluate emerging clinical trial data with the second-generation tyrosine kinase inhibitors, and assess how these agents may modify existing RCC treatment algorithms.. . . . . 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.

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

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Thomas E Hutson, DO, PharmD	4 3 2 1	4 3 2 1
Walter Stadler, MD	4 3 2 1	4 3 2 1
Brian I Rini, MD	4 3 2 1	4 3 2 1
Nicholas J Vogelzang, 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 faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:

⬭ MD ⬭ DO ⬭ PharmD ⬭ NP ⬭ 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 Credits™*. 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: .....

RCCUSE09

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 CME.ResearchToPractice.com.

Renal Cell Cancer™

U P D A T E

Editor	Neil Love, MD
Managing Editor and CME Director	Kathryn Ault Ziel, PhD
Scientific Director	Richard Kaderman, PhD
Senior Director, Medical Affairs	Aviva Asnis-Alibozek, PA-C, MPAS
Writer	Douglas Paley
Continuing Education Administrator for Nursing	Sally Bogert, RNC, WHCNP
Content Validation	Margaret Peng Erin Wall Clayton Campbell Gloria Kelly, PhD
Director, Creative and Copy Editing	Aura Herrmann
Creative Manager	Fernando Rendina
Graphic Designers	Jessica Benitez Jason Cunnius Tamara Dabney Deepti Nath
Senior Production Editor	Alexis Oneca
Traffic Manager	Tere Sosa
Copy Editors	Margo Harris David Hill Rosemary Hulce Kirsten Miller Pat Morrissey/Havlin Carol Peschke Susan Petrone
Production Manager	Tracy Potter
Audio Production	Frank Cesarano
Web Master	John Ribeiro
Faculty Relations Manager	Melissa Vives
Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: DrNeilLove@ResearchToPractice.com
For CME/CNE Information	Email: CE@ResearchToPractice.com

Renal Cell Cancer™

UPDATE

This program is supported by an educational grant from GlaxoSmithKline.

Research To Practice®

Cosponsored by Research To Practice and City of Hope.

Last review date: December 2009
Release date: December 2009
Expiration date: December 2010
Estimated time to complete: 3 hours