

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

David I Quinn, MBBS, PhD

Walter Stadler, MD

Mario Lacouture, MD

Bernard J Escudier, MD

CME
Certified



Subscribe to Podcasts or download MP3s of this program at RenalCellCancerUpdate.com

Renal Cell Cancer Update

A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF RENAL CELL CANCER UPDATE

The purpose of Issue 2 of *Renal Cell Cancer Update* is to support these global objectives by offering the perspectives of Drs Quinn, Stadler, Lacouture and Escudier on the integration of emerging clinical research data into the management of renal cell cancer.

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 2.75 *AMA PRA Category 1 Credit(s)*[™]. 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 listen to the CDs, review the monograph and complete the Post-test and Evaluation Form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. RenalCellCancerUpdate.com 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 here in [blue underlined text](#).

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

3 INTERVIEWS

David I Quinn, MBBS, PhD

University of Southern California
Los Angeles, California

7 Walter Stadler, MD

Professor of Medicine and Surgery
Director of Genitourinary Oncology
University of Chicago
Chicago, Illinois

11 Mario Lacouture, MD

Assistant Professor of Dermatology
Director, SERIES Clinic
Department of Dermatology
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

14 Bernard J Escudier, MD

Head of Immunotherapy Unit
Department of Medical Oncology
Institut Gustave Roussy
Villejuif, France

18 POST-TEST

19 EVALUATION FORM

If you would like to discontinue your complimentary subscription to *Renal Cell Cancer Update*, please email us at Info@ResearchToPractice.com, call us at (800) 648-8654 or fax us at (305) 377-9998. Please include your full name and address, and we will remove you from the mailing list.

IN THIS ISSUE OF *RENAL CELL CANCER UPDATE*

- ▶ First results presented at ASCO 2007 from the AVOREN trial evaluating bevacizumab with interferon in first-line therapy of metastatic disease: Potential impact on current nonprotocol decision-making
- ▶ Dose-escalation study of sorafenib reveals surprising results at ASCO 2007
- ▶ The SERIES Clinic at Northwestern University focusing on patients with dermatologic toxicities from emerging biologic agents

CONTENT VALIDATION AND DISCLOSURES

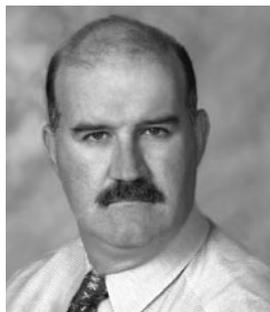
Research To Practice is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved by a peer review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

The scientific staff and consultants for Research To Practice are involved in the development and review of content for educational activities and report the following real or apparent conflicts of interest, either current or within the past 12 months, for themselves (or their spouses/partners) that have been resolved through a peer review process: John Brebner, Clayton Campbell, Karen Green, MD, Anne Jacobson, MPH, Richard Kaderman, PhD, Neil Love, MD, Douglas Paley, Michelle Paley, MD, Margaret Peng, Lilliam Sklaver Poltorack, PharmD, Ginelle Suarez, Chris Thomson, MD, MS, Erin Wall and Kathryn Ault Ziel, PhD — no real or apparent conflicts of interest to report; Aviva Asnis-Alibozek, PA-C, MPAS — salary: AstraZeneca Pharmaceuticals LP; shareholder of AstraZeneca Pharmaceuticals LP; Marie Bialek, PharmD — Freelance/Contract Medical Writer: Janssen Pharmaceutica Products LP, McNeil Consumer & Specialty Pharmaceuticals; salary (spouse): AstraZeneca Pharmaceuticals LP; Sally Bogert, RNC, WHCNP — shareholder of Amgen Inc and Genentech BioOncology. Research To Practice receives education grants from Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Biogen Idec, Genentech BioOncology/OSI Pharmaceuticals Inc, Genomic Health Inc, GPC Biotech, Roche Laboratories Inc and Sanofi-Aventis, who have no influence on the content development of our educational activities.

In addition, the following faculty (and their spouses/partners) have reported real or apparent conflicts of interest that have been resolved through a peer review process:

Dr Quinn — Consulting Fees and Contracted Research: Bayer Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Genentech BioOncology, Pfizer Inc; Fees For Non-CME Services Received Directly from Commercial Interest or Their Agents: Bayer Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Genentech BioOncology, Pfizer Inc. **Dr Stadler** — Consulting Fees and Contracted Research: Amgen Inc, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc; Ownership Interest: Abbott Laboratories. **Dr Lacouture** — Consulting Fees and Contracted Research: Amgen Inc, Bayer Pharmaceuticals Corporation, Genentech BioOncology. **Dr Escudier** — Consulting Fees: Bayer Pharmaceuticals Corporation, GlaxoSmithKline, Innate Pharma, Roche Laboratories Inc, Wyeth.

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 grantors.



INTERVIEW

David I Quinn, MBBS, PhD

Dr Quinn is from the University of Southern California in Los Angeles, California.

Tracks 1-17

- | | |
|---|--|
| Track 1 Clinical implications of AVOREN: Interferon- α 2a with or without bevacizumab as first-line therapy for metastatic renal cell cancer (mRCC) | Track 10 Treatment algorithm for patients with good-risk mRCC |
| Track 2 Clinical use of bevacizumab, sorafenib or sunitinib | Track 11 CALGB-90206: Phase III trial of interferon- α 2b with or without bevacizumab for patients with advanced RCC |
| Track 3 Thyroid function abnormalities associated with sorafenib and sunitinib | Track 12 Response to a second tyrosine kinase inhibitor (TKI) after progression on initial TKI therapy |
| Track 4 Defining poor-, intermediate- and good-risk disease | Track 13 Phase II dose-escalation trial with sorafenib |
| Track 5 Temsirolimus in patients with poor-risk mRCC | Track 14 Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access trial |
| Track 6 Temsirolimus in patients with good-risk mRCC | Track 15 Sunitinib expanded access trial |
| Track 7 Bevacizumab, sorafenib or sunitinib in patients with poor-risk mRCC | Track 16 Clinical trials evaluating combination and sequential therapeutic strategies |
| Track 8 Biologic rationale for differences in response to agents in poor-versus good-risk disease | Track 17 Adjuvant clinical trials in RCC |
| Track 9 Management of poor-risk disease in patients progressing on temsirolimus | |

Select Excerpts from the Interview

Tracks 1, 10

► **DR LOVE:** Would you discuss the clinical implications of data from the AVOREN trial presented at ASCO 2007 (Escudier 2007a)?

► **DR QUINN:** The AVOREN trial was a randomized Phase III study that evaluated patients with previously untreated metastatic clear cell carcinoma. Patients were randomly assigned to receive interferon three times a week in combina-

tion with either placebo or bevacizumab. Overall survival was the primary endpoint.

A doubling in progression-free survival occurred among patients who received bevacizumab with interferon compared to interferon with placebo. However, prior to the release of these data, interferon usage in the United States had dropped to virtually zero, so the AVOREN data raise the question of where interferon fits into the equation.

For the practitioner wanting to use bevacizumab, the question is whether to combine it with interferon in the first line or consider data from Phase II studies, such as the study presented by Dr Bukowski last year in which they evaluated bevacizumab alone versus bevacizumab with erlotinib and found no advantage to adding erlotinib (Bukowski 2006). However, in the bevacizumab-alone arm, the progression-free survival rate was approximately eight months. If one considers the data with the angiogenesis inhibitors, progression-free survival is between six and 11 months, depending on the setting.

In the first-line setting in this category, we have a choice of agents: sorafenib, sunitinib and bevacizumab — whether alone or in combination. A practitioner could pick any one of these, and one could argue that it doesn't matter which angiogenesis inhibitor you start with.

► **DR LOVE:** Bottom line, currently what are your first-, second- and third-line therapies for patients with good-risk renal cell carcinoma?

► **DR QUINN:** Currently, I start the patient on either sorafenib or sunitinib. The question is which TKI to start with. Sunitinib has the best data in the first-line setting (Motzer 2007), and data from a randomized Phase II study evaluating sorafenib did not indicate that sorafenib had greater activity than interferon, although sorafenib did allow for a better quality of life (Escudier 2007b).

I believe older patients may tolerate sorafenib better than sunitinib because of fatigue issues. However, if I have a patient that cannot tolerate hand-foot syndrome because he or she has a dexterous job — playing in the orchestra, for example — then I steer away from sorafenib and administer sunitinib. After that, I apply an algorithm based on the disease control and how well the patient is tolerating the medication.

Some of the patients develop a rash, hand-foot syndrome or fatigue. In that setting, if I have a patient with stable disease or only a suggestion of progression, my threshold is now low for switching to the other TKI.

My approach is to “mix and match” based on the side effects experienced by the individual patient. We have evidence from the clinic and published in abstracts, but not tested specifically in studies, that sequential TKI inhibition can produce responses in patients with disease that was resistant or stable (Dham 2007; Sablin 2007).

Considering the data on bevacizumab/interferon- α 2a that were presented at ASCO 2007 (Escudier 2007a), if I started with one of the TKIs and the patient

didn't do well, I might recommend a three-weekly infusion of bevacizumab. However, I don't believe that is standard.

Track 13

▶ **DR LOVE:** Can you discuss the Amato paper on sorafenib dose escalation that was presented at ASCO 2007?

▶ **DR QUINN:** It is fascinating. The patients started on a standard dose of sorafenib — 400 milligrams twice a day for one month. If they did not develop particular toxicities, the dose was escalated to 600 milligrams twice a day and then after another month to 800 milligrams twice a day.

A majority of the patients were able to receive the total dose of 1,600 milligrams a day. Dr Amato reported a decent-sized, albeit Phase II, dose-escalation trial with a complete and partial response rate of 55 percent, which is high (Amato 2007; [1.1]). This study suggests that a proportion of patients need to have an escalation of sorafenib to maximize the response.

In reviewing this, Dr Figlin noted that we haven't yet seen this with the TKIs. In the TARGET study, which might be considered a standard for sorafenib, the investigator-reported response rate was 10 percent (Escudier 2007b).

1.1

A Phase II Trial of Inpatient Dose-Escalated Sorafenib in Patients with Metastatic Renal Cell Cancer

	N (%)	Months (95% CI)
Median overall survival	44 (100)	11.47 (4.27-17.37)
Median PFS		
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.

SOURCE: Amato RJ et al. *Proc ASCO* 2007; [Abstract 5026](#).

Track 14

▶ **DR LOVE:** Can you discuss the papers presented at ASCO 2007 from the Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access program?

▶ **DR QUINN:** It appears that sorafenib has activity in the first-line setting, based on the report from the ARCCS study (Knox 2007; Ryan 2007). This runs counter to the randomized Phase II comparison of sorafenib and interferon suggesting that sorafenib was not so good in the first-line setting (Szczylik 2007). The question is, which set of data do you believe? I believe we have to

evaluate it in clinical practice, and my clinical practice in the first-line setting runs closer to the ARCCS data than to the randomized Phase II study.

The other presentations from the ARCCS trial were on selected groups of patients. Among the patients with brain metastases that had been previously irradiated or surgically removed, no CNS hemorrhages were recorded and the rates of disease benefit were similar (Henderson 2007). The other big set of data demonstrated activity in nonclear cell types of cancer, particularly papillary and chromophobe subtypes (Stadler 2007). ■

SELECT PUBLICATIONS

Amato RJ et al. **A phase II trial of intra-patient dose-escalated sorafenib in patients (pts) with metastatic renal cell cancer (MRCC).** *Proc ASCO* 2007;[Abstract 5026](#).

Bajetta E et al. **Renal cell cancer and sorafenib: Skin toxicity and treatment outcome.** *Tumori* 2007;93(2):201-3. [Abstract](#)

Bukowski RM et al. **Final results of the randomized phase III trial of sorafenib in advanced renal cell carcinoma: Survival and biomarker analysis.** *Proc ASCO* 2007;[Abstract 5023](#).

Bukowski RM et al. **Results of a randomized phase II trial of bevacizumab +/- erlotinib in mRCC.** Presentation. ASCO 2006;[Abstract 4523](#).

Choueiri TK et al. **Clinical factors associated with outcome in patients with metastatic clear-cell renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy.** *Cancer* 2007;110(3):543-50. [Abstract](#)

Dham A, Dudek AZ. **Sequential therapy with sorafenib and sunitinib in renal cell carcinoma.** *Proc ASCO* 2007;[Abstract 5106](#).

Drabkin HA et al. **The Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access trial: Safety and efficacy in patients (pts) with prior bevacizumab (BEV) treatment.** *Proc ASCO* 2007;[Abstract 5041](#).

Escudier B et al. **A randomized, controlled, double-blind phase III study (AVOREN) of bevacizumab/interferon- α 2a vs placebo/interferon- α 2a as first-line therapy in metastatic renal cell carcinoma.** *Proc ASCO* 2007a;[Abstract 3](#).

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

Henderson CA et al. **The Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access trial: Subset analysis of patients (pts) with brain metastases (BM).** *Proc ASCO* 2007;[Abstract 15506](#).

Knox JJ et al. **The Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access trial in North America: Safety and efficacy.** *Proc ASCO* 2007;[Abstract 5011](#).

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

Ryan CW et al. **The Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access trial: Long-term outcomes in first-line patients (pts).** *Proc ASCO* 2007;[Abstract 5096](#).

Sablin MP et al. **Sequential use of sorafenib and sunitinib in renal cancer: Retrospective analysis in 90 patients.** *Proc ASCO* 2007;[Abstract 5038](#).

Stadler WM et al. **The Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access trial: Safety and efficacy in patients (pts) with non-clear cell (NCC) renal cell carcinoma (RCC).** *Proc ASCO* 2007;[Abstract 5036](#).

Szczylik C et al. **Randomized phase II trial of first-line treatment with sorafenib versus interferon in patients with advanced renal cell carcinoma: Final results.** *Proc ASCO* 2007;[Abstract 5025](#).



INTERVIEW

Walter Stadler, MD

Dr Stadler is Professor of Medicine and Surgery and Director of Genitourinary Oncology at the University of Chicago in Chicago, Illinois.

Tracks 1-14

- | | | | |
|----------------|---|-----------------|---|
| Track 1 | AVOREN: Interferon- α 2a with or without bevacizumab as first-line therapy in mRCC | Track 8 | Use of the mTOR inhibitor temsirolimus in patients with poor-risk RCC |
| Track 2 | Use of bevacizumab monotherapy in RCC | Track 9 | Increasing doses of sunitinib or sorafenib in clinical practice |
| Track 3 | Bevacizumab-associated side effects and toxicity | Track 10 | The Randomized Discontinuation clinical trial design |
| Track 4 | Potential antitumor mechanism(s) of bevacizumab | Track 11 | Studying combinations of molecularly targeted agents in RCC |
| Track 5 | Treatment algorithm for patients with mRCC | Track 12 | Management of VEGF TKI-associated toxicities |
| Track 6 | Incorporation of bevacizumab into the management of mRCC | Track 13 | Use of combined therapy in RCC |
| Track 7 | ECOG-E2805: Adjuvant sunitinib, sorafenib or placebo in resected RCC | Track 14 | Targeting novel pathways in RCC |

Select Excerpts from the Interview

Track 4

► **DR LOVE:** What do we know about the mechanism of action of bevacizumab in renal cell cancer?

► **DR STADLER:** Kidney cancer is distinctive in that these tumors express one of the highest levels of VEGF.

This is directly related to the pathophysiology of this tumor type, which is thought to involve inactivation of the von Hippel-Lindau (VHL) pathway leading to upregulation of the HIF transcription factor, which in turn leads to upregulation of VEGF.

These data, which were obtained from expression profiling, suggest a direct anti-angiogenic effect as the mechanism of action of bevacizumab in kidney cancer.

Tracks 5-6

▶ **DR LOVE:** What's your general algorithm right now for first- and second-line therapy in metastatic disease?

▶ **DR STADLER:** For patients with good prognoses, the most mature front-line data are with the VEGF receptor TKIs — specifically with sunitinib — so that would be my choice for first-line therapy. That's also driven by the fact that as of now, bevacizumab has not received full regulatory approval for treatment. I believe that once bevacizumab receives approval, whether one uses the TKIs, bevacizumab or temsirolimus first line remains an open question.

In the second line, we enroll patients on one of our trials. We're considering the use of alternative VEGF receptor-targeting agents but also have a trial evaluating combinations of agents with bevacizumab. One of the combinations we're studying is bevacizumab with gemcitabine and capecitabine, based on earlier work we conducted at our institution and through the CALGB.

▶ **DR LOVE:** How would you ideally use it in renal cell cancer?

▶ **DR STADLER:** Using it in the front line makes sense, especially for patients with good prognoses. My recommendation would be to use bevacizumab with interferon because that's what the Phase III data tell us (Escudier 2007).

▶ **DR LOVE:** How would you compare quality of life using sorafenib or sunitinib versus bevacizumab as a single agent?

▶ **DR STADLER:** I believe the toxicities of sorafenib and sunitinib are broader than the toxicities of bevacizumab, in that the TKIs also produce skin and gastrointestinal (GI) toxicities. Certainly some patients have more difficulty with some of these skin and bowel toxicities from the TKIs, but many of our patients have tolerated these treatments for long periods.

Track 7

▶ **DR LOVE:** Would you discuss the ongoing adjuvant trial evaluating sorafenib and sunitinib?

▶ **DR STADLER:** This is an ECOG-sponsored trial (ECOG-E2805) for patients with high-risk cancer after surgery and no evidence of metastatic disease (2.1). Patients are randomly assigned to one year of sorafenib versus sunitinib versus placebo, with disease-free survival as the primary endpoint. The study also includes an opportunity to register patients prior to surgery in order to collect tumor specimens and evaluate potential molecular predictive markers.

▶ **DR LOVE:** In this study, is it going to be evident which patients are receiving sorafenib or sunitinib and which patients are receiving placebo?

▶ **DR STADLER:** I believe there is a concern that this study is not going to be truly blinded. Obviously if a patient has significant skin or diarrheal toxicities, it's unlikely that the patient is receiving placebo. However, we've learned

in conducting placebo-controlled trials that our accuracy in predicting which agent the patient was receiving is much less than we thought it would be.

► **DR LOVE:** Do you have any predictions as to the outcome of the trial?

► **DR STADLER:** I'm hopeful that the data will show that one of the oral TKIs will delay disease progression.

2.1

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

Protocol ID: ECOG-E2805
Target Accrual: 1,332



Select Eligibility Criteria

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

Target Accrual: 1,332
Current Accrual: 407 (8/4/07)
Date Activated: April 24, 2006

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, August 2007; www.ctsu.org.

Track 11

► **DR LOVE:** What are some of the clinical trial concepts being considered in renal cell cancer with regard to combinations of biologics?

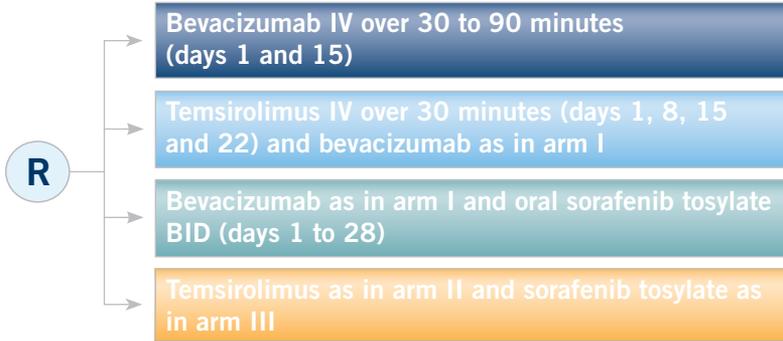
► **DR STADLER:** A lot of interest has been expressed with regard to combining VEGF pathway targeted agents — either the TKIs or bevacizumab — with the mTor (mammalian target of rapamycin) inhibitors, such as sirolimus, temsirolimus and everolimus. There is great interest in combining these classes of agents because they work on different but related pathways. ECOG is launching a randomized Phase II trial with multiple combinations, including bevacizumab, sorafenib and temsirolimus in various combinations (2.2).

I believe the biggest question is whether these combinations will prove to be any better than using the drugs in sequence, because we know that the combinations increase toxicity. ■

2.2

Phase II Randomized Study of Bevacizumab, Sorafenib Tosylate and Temsirolimus for Patients with Metastatic Renal Cell Carcinoma

Protocol ID: ECOG-E2804
Target Accrual: 360 (Open)



In all arms, treatment repeats q28d in the absence of disease progression or unacceptable toxicity.

Select Eligibility Criteria

- Histologically confirmed clear cell renal cell carcinoma
- Measurable metastatic disease
- Not curable by standard radiation therapy or surgery

Study Contacts

Eastern Cooperative Oncology Group
Keith Flaherty, MD, Protocol Chair
Tel: 215-662-8624
David McDermott, MD, Protocol Co-Chair
Tel: 617-667-9920

SOURCE: NCI Physician Data Query, June 2007.

SELECT PUBLICATIONS

Escudier B et al. **A randomized, controlled, double-blind phase III study (AVOREN) of bevacizumab/interferon- α 2a vs placebo/interferon- α 2a as first-line therapy in metastatic renal cell carcinoma.** *Proc ASCO* 2007; [Abstract 3](#).

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](#).

Klatte T et al. **Understanding the natural biology of kidney cancer: Implications for targeted cancer therapy.** *Rev Urol* 2007;9(2):47-56. [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](#)

Stadler WM et al. **Successful implementation of the randomized discontinuation trial design: An application to the study of the putative antiangiogenic agent carboxyaminoimidazole in renal cell carcinoma — CALGB 69901.** *J Clin Oncol* 2005;23(16):3726-32. [Abstract](#)

Vogelzang N. **Targeted therapies for renal cell carcinoma: A new standard of care.** Available at: www.medscape.com/viewarticle/541604.



INTERVIEW

Mario Lacouture, MD

Dr Lacouture is Assistant Professor of Dermatology and Director of the SERIES Clinic in the Department of Dermatology at Northwestern University's Feinberg School of Medicine in Chicago, Illinois.

Tracks 1-19

- | | | | |
|-----------------|--|-----------------|---|
| Track 1 | SERIES (Skin and Eye Reactions to Inhibitors of EGFR and kinaseS) Clinic | Track 11 | Dermatologic toxicities associated with EGFR inhibitors |
| Track 2 | Hand-foot skin reactions and anticancer therapy | Track 12 | Implications of dermatologic side effects for the use of agents in the adjuvant setting |
| Track 3 | Case report of hand-foot and stump syndrome associated with sorafenib | Track 13 | Algorithm for the management of EGFR-related dermatologic toxicities |
| Track 4 | Time course and management of hand-foot syndrome associated with sorafenib and sunitinib | Track 14 | Mechanism of EGFR-related dermatologic toxicity |
| Track 5 | Prophylaxis of hand-foot syndrome associated with sorafenib and sunitinib | Track 15 | Correlation between skin reactions and response to EGFR inhibitors |
| Track 6 | Additional dermatologic toxicities associated with sorafenib and sunitinib | Track 16 | Frequently asked questions about dermatologic reactions |
| Track 7 | Alopecia associated with sorafenib and sunitinib | Track 17 | Counseling patients about dermatologic toxicities |
| Track 8 | Topical agents for treating dermatologic reactions associated with sorafenib and sunitinib | Track 18 | Development of a specialty interest in dermatologic toxicities of cancer treatments |
| Track 9 | Quality-of-life issues associated with hand-foot skin reactions | Track 19 | Dermatologic toxicities associated with pegylated doxorubicin and docetaxel |
| Track 10 | Dermatologic toxicities associated with interferon | | |

Select Excerpts from the Interview

Track 1

► **DR LOVE:** Can you discuss the evolution of the SERIES (Skin and Eye Reactions to Inhibitors of EGFR and kinaseS) Clinic?

► **DR LACOUTURE:** Our interest in the dermatological toxicities of novel anticancer drugs began with the knowledge that many of these agents are

otherwise largely devoid of systemic or hematopoietic side effects and, therefore, the high frequency of complaints affecting the skin, hair and nails make these side effects of the utmost importance.

We had to take into consideration that these could be life-saving or life-prolonging treatments. Our goals were to better understand and manage these dermatological side effects and to try to maintain patients on therapy for as long as possible.

Fortunately, we were able to fulfill these goals by providing rapid access for patients. We try to see patients the same day or the next day and treat them for side effects to be able to maintain them on anticancer therapy (Lacouture 2006).

Tracks 2, 4

▶ **DR LOVE:** What are the skin toxicities you have observed with sorafenib and sunitinib?

▶ **DR LACOUTURE:** Dermatological side effects are seen with high frequency. Data from Phase III randomized studies indicated that sorafenib led to a hand-foot skin reaction in 30 percent of patients, with Grade III to Grade IV severity in only five percent (Escudier 2007).

With sunitinib, the development of the hand-foot skin reaction occurred in 20 percent of patients, and of those cases only five percent were Grade III to IV in severity (Motzer 2007).

Hand-foot syndrome also occurs with other agents, such as fluorouracil or pegylated doxorubicin. However, these seem to be clinically and histologically distinct from the hand-foot skin reaction occurring with sorafenib and sunitinib.

With more conventional agents, you have swelling, redness and pain diffusely through the palms and soles. With sorafenib and sunitinib, you have a thickening of the skin. This thickening, when it is subject to pressure, leads to bleeding underneath the thickened areas, causing significant pain for the patient.

▶ **DR LOVE:** What's the typical time course of these symptoms and signs, and how do you manage them?

▶ **DR LACOUTURE:** The hand-foot skin reaction tends to develop after the first month of therapy. With sorafenib, for which an administration of 400 milligrams twice daily is uninterrupted, you tend to see it earlier than with sunitinib, as the sunitinib regimen allows for a two-week drug holiday.

Patients are able to recover from the tenderness and pain during that two-week drug holiday.

Flushing — the red face and the seborrheic dermatitis-like reaction — occurs within the first two to four weeks. Hand-foot skin reactions usually occur

later, and they tend to become worse over time if the symptoms are not managed.

For management, we have used high-concentration urea-containing preparations, such as urea 40 percent creams.

These are keratolytics, so they disrupt the outer layer of the skin, the stratum corneum. They seem to thin out that thickened skin layer that may be responsible for the increased pressure leading to the pain.

We also prescribe high-potency topical steroids, such as clobetasol ointment, as this will minimize the proliferation or the division of those skin cells. It will also decrease the underlying inflammation.

Track 16

► **DR LOVE:** What are some common questions you receive from medical oncologists about these syndromes?

► **DR LACOUTURE:** One question is whether the rash that occurs secondary to sorafenib correlates with response. Some evidence suggests that sorafenib-induced rash may correlate with survival, perhaps indicating greater bioavailability.

Another question is whether the rash secondary to the TKIs is similar to that occurring secondary to the EGFR inhibitors. However, the in vitro inhibitory profiles of these agents are completely different.

Therefore, the rash secondary to EGFR inhibitors should not be confused with the rash secondary to TKIs. It is completely different, both in its clinical presentation and in its response to therapy with doxycycline or with tetracycline antibiotics, which are ineffective against the rash associated with the TKIs. ■

SELECT PUBLICATIONS

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

Lacouture ME et al. **Patterns of management of rash associated with epidermal growth factor receptor inhibitors (EGFRIs): A national practice survey.** *Proc ASCO* 2007;[Abstract 14081](#).

Lacouture ME et al. **The SERIES clinic: An interdisciplinary approach to the management of toxicities of EGFR inhibitors.** *J Support Oncol* 2006;4(5):236-8. No abstract available

Lynch TJ Jr et al. **Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: An evolving paradigm in clinical management.** *Oncologist* 2007;12(5):610-21. [Abstract](#)

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

Wagner L et al. **Development of a functional assessment of side-effects to therapy (FAST) questionnaire to assess dermatology-related quality of life in patients treated with EGFR inhibitors (EGFRI): The FAST-EGFRI.** *Proc ASCO* 2007;[Abstract 19532](#).



INTERVIEW

Bernard J Escudier, MD

Dr Escudier is Head of the Immunotherapy Unit in the Department of Medical Oncology at the Institut Gustave Roussy in Villejuif, France.

Tracks 1-10

- | | | | |
|----------------|---|-----------------|--|
| Track 1 | Background and design of AVOREN: Phase III trial of interferon- α 2a with or without bevacizumab as first-line therapy in mRCC | Track 6 | TARGET trial of sorafenib as second-line therapy for patients with RCC |
| Track 2 | AVOREN trial: Duration of therapy and incidence of side effects | Track 7 | Emerging Phase II data with sorafenib in RCC |
| Track 3 | Clinical use of bevacizumab in patients with mRCC | Track 8 | Treatment algorithm for patients with mRCC |
| Track 4 | Clinical trial strategies incorporating TKIs with bevacizumab in RCC | Track 9 | Discussion of an adjuvant bevacizumab trial in RCC |
| Track 5 | Clinical use of temsirolimus or sorafenib in patients with mRCC | Track 10 | Side effects associated with sorafenib and sunitinib |

Select Excerpts from the Interview

Track 1

► **DR LOVE:** Would you discuss the background and design of the AVOREN trial (Escudier 2007a)?

► **DR ESCUDIER:** Bevacizumab has previously been shown to be active in kidney cancer. The first study was presented at ASCO in 2002 (Yang 2002) and demonstrated that when you administer bevacizumab (10 mg/kg every two weeks) to patients who have failed high-dose IL-2, you can achieve a significant improvement in progression-free survival (PFS) compared to placebo.

At ASCO 2006, Ron Bukowski presented an interesting study (Bukowski 2006), which aimed to determine whether adding erlotinib to bevacizumab could improve PFS. That trial turned out to be negative, but in the bevacizumab-alone arm, PFS was 8.5 months among previously untreated patients. Together, these observations suggested that bevacizumab was probably an active drug in kidney cancer — that was our hypothesis when we started our trial.

A lot of discussion ensued about what the control arm should be. At the time, interferon was the standard, so we decided to add bevacizumab to interferon, and to avoid any bias, we chose to conduct a double-blind, randomized, controlled study with a placebo arm (3.1).

This is interesting, and it's different from the CALGB study (CALGB-90206; Rini 2004), which doesn't have a placebo arm, making that study much more difficult to analyze.

We elected to use an interferon dosage that was utilized by Motzer in his sunitinib study (Motzer 2007) and to add bevacizumab at 10 mg/kg every two weeks. Our initial goal was to show an improvement in overall survival, so that was our primary endpoint.

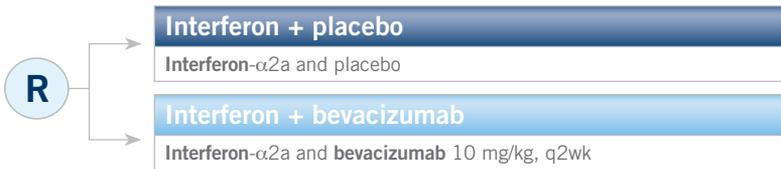
Our data with interferon show that overall survival should be in the range of 13 months, and our statistical hypothesis was that overall survival would increase from 13 to 17 months. We needed 650 patients to demonstrate this difference with an acceptable hazard ratio.

We opted to perform the final overall survival analysis at 445 deaths and a planned interim analysis at 250 deaths. At that time it was specified that we would also perform a final PFS analysis, and depending on the results, the DSMB would recommend unblinding the study if it was positive.

3.1

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

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



Select Eligibility Criteria

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

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

Tracks 2-3

► **DR LOVE:** Can you discuss the results from the trial?

► **DR ESCUDIER:** According to investigator observation, the response rate increased with the addition of bevacizumab — overall response was 31 percent

Investigator-Assessed Tumor Response to Interferon with or without Bevacizumab as First-Line Treatment of Metastatic Renal Cell Carcinoma (AVOREN Trial)

Response	IFN + placebo (n = 289)	IFN + bevacizumab (n = 306)	p-value
Overall response rate*	13%	31%	<0.0001
Complete response	2%	1%	<0.0001
Partial response	11%	30%	<0.0001
Median duration of response	11 mo	13 mo	NR
Median progression-free survival	5.4 mo	10.2 mo	<0.0001
Median duration of stable disease	7 mo	10 mo	NR

NR = not reported

* Patients with measurable disease only

SOURCE: Escudier B et al. *Proc ASCO* 2007a; [Abstract 3](#).

among those who received interferon/bevacizumab and 13 percent among those who received interferon/placebo (3.2). The analysis showed a doubling of PFS, from 5.4 months to 10.2 months.

When we assessed the different subgroups, we noticed a significant benefit in the favorable risk group, but the benefit was even more important in the intermediate prognostic group, in which the PFS went from 4.5 to 10.2 months (Escudier 2007a).

In the intermediate-risk group, we believe that interferon has little — if any — activity, based on the last study we presented, so we believe that the majority of the effects we have seen in this study are due to the activity of bevacizumab in this group.

► **DR LOVE:** Can you review the safety and tolerability data?

► **DR ESCUDIER:** More Grade III and IV adverse events were recorded in the bevacizumab/interferon arm than in the placebo/interferon arm (60 percent versus 45 percent of the patients, respectively).

The incidence of fatigue was a little higher in the bevacizumab arm, perhaps due to the additive effects of the drug but perhaps also due to the fact that exposure to interferon was longer in the combination arm.

In terms of bevacizumab-associated side effects, the observed rate of proteinuria was 6.5 percent. The rates of hemorrhage and gastrointestinal perforation were 3.3 and 1.5 percent respectively.

The incidence of death that was not due to progressive disease was two percent in both arms. Of the eight patients in the bevacizumab arm who died, three deaths were possibly related to bevacizumab.

We observed an incidence of 3.9 percent of Grade III hypertension — similar to what we usually see with this type of agent.

► **DR LOVE:** What does this mean for clinical practice? How do you think people will react to these data in terms of the treatment algorithm for metastatic disease?

► **DR ESCUDIER:** Interferon with bevacizumab is now one alternative for first-line therapy in the metastatic setting. When you view the data with the AVOREN regimen compared to sunitinib, you see that we are in the same range of response for PFS (Motzer 2007).

In my mind, and perhaps the minds of investigators, side effects are probably a little less troublesome with this regimen than with sunitinib.

The question now is, what is the effect of interferon in this regimen? Some physicians will consider bevacizumab the agent that provides all the benefit. At this point, it's fair to say we don't know.

In previous bevacizumab data, PFS was lower than what was recorded with this regimen (Yang 2003; Bukowski 2006), so is interferon necessary to this result? Perhaps it is. Either way, I believe that in Europe we will consider this combination as a standard, and it will compete with sunitinib.

In the United States, my prediction is that many people will consider bevacizumab alone to be enough and that it will compete largely with sunitinib. I would not be surprised if a number of people believe it's better to start with bevacizumab alone — because it's easy to administer and has fewer side effects than sunitinib alone — and to keep sunitinib for the second line. ■

SELECT PUBLICATIONS

Bukowski RM et al. **Bevacizumab with or without erlotinib in metastatic renal cell carcinoma (RCC).** *Proc ASCO* 2006; [Abstract 4523](#).

Escudier B et al. **A randomized, controlled, double-blind phase III study (AVOREN) of bevacizumab/interferon- α 2a vs placebo/interferon- α 2a as first-line therapy in metastatic renal cell carcinoma.** *Proc ASCO* 2007a; [Abstract 3](#).

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

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

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

Rini BI et al. **Cancer and Leukemia Group B 90206: A randomized phase III trial of interferon-alpha or interferon-alpha plus anti-vascular endothelial growth factor antibody (bevacizumab) in metastatic renal cell carcinoma.** *Clin Cancer Res* 2004;10(8):2584-6. [Abstract](#)

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

Yang JC et al. **A randomized double-blind placebo-controlled trial of bevacizumab (anti-VEGF antibody) demonstrating a prolongation in time to progression in patients with metastatic renal cancer.** *Proc ASCO* 2002; [Abstract 15](#).

QUESTIONS (PLEASE CIRCLE ANSWER):

1. Data from uncontrolled studies have demonstrated that in patients whose disease did not respond to one TKI, a second TKI could lead to stable disease or a partial response.
 - a. True
 - b. False
2. In a Phase II dose-escalation trial of sorafenib, the highest dose administered was _____.
 - a. 400 milligrams twice a day
 - b. 800 milligrams twice a day
 - c. 1,600 milligrams twice a day
 - d. 3,200 milligrams twice a day
3. Hand-foot skin reactions tend to occur within _____ of treatment initiation with sorafenib or sunitinib.
 - a. One to two days
 - b. One to two weeks
 - c. One to two months
4. Both sorafenib and sunitinib may lead to Grade III and IV hand-foot skin reactions in approximately ____ percent of patients.
 - a. One
 - b. Five
 - c. 10
 - d. 15
5. In the AVOREN trial of interferon with or without bevacizumab for metastatic renal cell carcinoma, overall response was _____ percent among patients who received bevacizumab/interferon.
 - a. 13
 - b. 31
 - c. 29
 - d. 33
6. In the AVOREN trial, progression-free survival among patients who received interferon with bevacizumab was double that of patients who received interferon alone.
 - a. True
 - b. False
7. Rash secondary to EGFR inhibitors is similar to rash secondary to multitargeted kinase inhibitors in both clinical presentation and response to therapy.
 - a. True
 - b. False
8. The recently approved ECOG Phase II trial for advanced renal cell carcinoma (E2804) will randomly assign patients to which combination of biologics?
 - a. Bevacizumab with or without temsirolimus
 - b. Bevacizumab with sorafenib
 - c. Temsirolimus with sorafenib
 - d. All of the above
 - e. None of the above
9. Of the following, all are considered mTOR inhibitors except _____.
 - a. Bevacizumab
 - b. Everolimus
 - c. Sirolimus
 - d. Temsirolimus
10. In the AVOREN trial, Grade III/IV adverse events were observed in ____ percent of the patients receiving bevacizumab/interferon and ____ percent of the patients receiving placebo/interferon.
 - a. 60, 15
 - b. 60, 25
 - c. 60, 30
 - d. 60, 45

EVALUATION FORM

Renal Cell Cancer Update — Issue 2, 2007

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this Evaluation Form. A certificate of completion will be issued upon receipt of your completed Post-test and Evaluation Form.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor N/A = Not applicable to this issue of *RCCU*

GLOBAL LEARNING OBJECTIVES

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
David I Quinn, MBBS, PhD	5 4 3 2 1	5 4 3 2 1
Walter Stadler, MD	5 4 3 2 1	5 4 3 2 1
Mario Lacouture, MD	5 4 3 2 1	5 4 3 2 1
Bernard J Escudier, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

- Objectives were related to overall purpose/goal(s) of activity. 5 4 3 2 1 N/A
- Related to my practice needs. 5 4 3 2 1 N/A
- Will influence how I practice. 5 4 3 2 1 N/A
- Will help me improve patient care. 5 4 3 2 1 N/A
- Stimulated my intellectual curiosity. 5 4 3 2 1 N/A
- Overall quality of material. 5 4 3 2 1 N/A
- Overall, the activity met my expectations. 5 4 3 2 1 N/A
- Avoided commercial bias or influence. 5 4 3 2 1 N/A

Which of the following audio formats of this program did you use?

- Audio CDs Downloaded MP3s from website

EVALUATION FORM

Renal Cell Cancer Update — Issue 2, 2007

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 2.75 AMA PRA Category 1 Credit(s)TM. 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:

Will the information presented cause you to make any changes in your practice?

Yes No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

.....

What other topics would you like to see addressed in future educational programs?

.....

What other faculty would you like to hear interviewed in future educational programs?

.....

Additional comments about this activity:

.....

FOLLOW-UP

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.

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation 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 Evaluation online at www.RenalCellCancerUpdate.com/CME.

Renal Cell Cancer™

U P D A T E

Editor/CME Director	Neil Love, MD
Managing Editor	Kathryn Ault Ziel, PhD
Scientific Director	Richard Kaderman, PhD
Senior Director, Medical Affairs	Aviva Asnis-Alibozek, PA-C, MPAS
Writers	Lillian Sklaver Poltorack, PharmD Douglas Paley Marie Bialek, PharmD Clayton Campbell Anne Jacobson, MPH
Continuing Education Administrator for Nursing	Sally Bogert, RNC, WHCNP
Content Validation	Margaret Peng John Brebner Ginelle Suarez Erin Wall
Director, Creative and Copy Editing	Aura Herrmann
Creative Manager	Fernando Rendina
Graphic Designers	Jason Cunnius Tamara Dabney Shantia Daniel Elisa Stambouli
Senior Production Editor	Alexis Oneca
Traffic Manager	Tere Sosa
Copy Editors	Dave Amber Margo Harris Rosemary Hulce Kirsten Miller Pat Morrissey/Havlin Carol Peschke Susan Petrone
Production Manager	Rena Chiarelli
Audio Production	Frank Cesarano
Web Master	John Ribeiro
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: NLove@ResearchToPractice.com
For CME Information	Email: CME@ResearchToPractice.com

Copyright © 2007 Research To Practice. All rights reserved.

The compact discs, Internet content and accompanying printed material are protected by copyright. No part of this program may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or utilizing any information storage and retrieval system, without written permission from the copyright owner.

The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their

own professional development. The information presented in this activity is not meant to serve as a guideline for patient management.

Any procedures, medications or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information and comparison with recommendations of other authorities.

Renal Cell Cancer™

U P D A T E

Copyright © 2007 Research To Practice.

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



Sponsored by Research To Practice.

Last review date: August 2007

Release date: August 2007

Expiration date: August 2008

Estimated time to complete: 2.75 hours