Renal Cell Cancer™

U P D A T E

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

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SPECIAL ISSUE

Proceedings from a Clinical Investigator Roundtable

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Renal Cell Cancer Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

An increased understanding of the biology of renal cell cancer (RCC) coupled with emerging clinical trial data has resulted in the availability of several new therapeutic options for patients. However, the treatment algorithm has become increasingly complex and the excitement accompanying the explosion of novel agents with proven efficacy in RCC has been somewhat tempered by a full appreciation of the unique tolerability challenges experienced by patients. Thus, practicing oncologists must maintain current knowledge of the benefits and risks of the multiple acceptable treatment approaches. To bridge the gap between research and patient care, this program features a roundtable discussion with leading investigators to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Evaluate the role of nephrectomy for patients presenting with metastatic RCC.
- Identify patients with RCC who may benefit from expectant observation, and consider factors affecting the timing of initial treatment.
- Apply the results of existing and emerging clinical research to the evidence-based selection of front-line and subsequent therapy for metastatic RCC.
- Compare and contrast the safety and tolerability of cytokine immunotherapy, multikinase inhibitors, mTOR inhibitors and VEGF monoclonal antibody therapy for RCC.
- Recommend supportive management strategies to effectively address the side effects of targeted treatments for RCC.
- Recognize indications for dose adjustment or discontinuation of multikinase inhibitor therapy, and assess the effect of both on ultimate treatment efficacy.
- Recall the scientific rationale for and early efficacy of novel investigational compounds demonstrating activity in RCC.
- Counsel appropriately selected patients with RCC about the availability of ongoing clinical trial participation.

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This program is supported by an educational grant from GlaxoSmithKline.

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Select Key Publications and Presentations Discussed in this Program

Hawkins RE et al. **An open-label extension study to evaluate safety and efficacy of pazopanib in patients with advanced renal cell carcinoma (RCC).** *Proc ASCO* 2009;Abstract 5110.

Houk BE et al. **Exposure-response of sunitinib in metastatic renal cell carcinoma (mRCC): A population pharmacokinetic/pharmacodynamic (PKPD) approach.** *Proc ASCO* 2007;Abstract 5027.

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.

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

Rini BI et al. **Neoadjuvant sunitinib in patients (pts) with unresectable primary renal cell carcinoma (RCC).** Genitourinary Cancers Symposium 2009;Abstract 288.

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.

Wood L et al. **Sunitinib in patients (pts) with unresectable primary renal cell carcinoma (RCC).** *Proc ASCO* 2009;Abstract 5096.

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EDITOR'S NOTE

Neil Love, MD

On a mission

Renal cell carcinoma (RCC) made an abrupt and dramatic entrance to the oncology main stage in January 2006 when Dr Robert Motzer published in the *JCO* stunning initial results of a Phase II study demonstrating robust antitumor activity of sunitinib in metastatic RCC as second-line therapy. What struck me most about that paper was a graphic I had not seen before but have come to love: A waterfall plot demonstrating that most patients in the study experienced tumor regression.

Dr Motzer's subsequent ASCO 2006 plenary presentation of a Phase III study demonstrating that sunitinib was superior to interferon as first-line therapy for mRCC basically changed the standard of care in this disease while also providing a prelude of what was to come. Since that memorable session, there has been a deluge of other salient RCC data sets involving a number of different agents, including sorafenib, temsirolimus, everolimus, bevacizumab and, more recently, pazopanib and axitinib.

The rapid addition of new treatment options and the sudden complexity of RCC systemic management has created a significant challenge for medical oncologists in practice, who are already paddling upstream through a torrent of other new information in more common diseases like breast, lung and colorectal cancer.

This audio program is part of an integrated "experiment in CME" (Figure 1) designed to scientifically determine the optimal method to keep these harried and heroic physicians up to date and informed as they attempt to provide compassionate, state-of-the-art care to people facing an often devastating downhill clinical course.

To begin this unique odyssey into the heart of RCC, we decided to talk to our "customers" — in this case oncologists from US Oncology, a group that not only provides a great deal of clinical care but also makes major contributions to clinical research (see the ASCO plenary dais this year, with Joyce O'Shaughnessy presenting yet another critical data set). Our content team spent hours chatting with these US Oncology physicians about what they wished to learn about RCC, and they also recorded dozens of cases and related clinical questions.

1 National Renal Cell Cancer Integrated Curriculum

Needs assessment interviews
(20 oncologists from US Oncology)

↓

Think Tank meeting

Faculty

- Michael B Atkins, MD
- Robert A Figlin, MD (project co-chair)
- Thomas E Hutson, DO, PharmD
- Eric Jonasch, MD
- Robert J Motzer, MD
- David I Quinn, MBBS, PhD

↓

Patterns of Care Study 1

↓

Mailing of Think Tank audio program
(along with two related email "5 Minute Journal Clubs")

↓

Mailing of interview audio program
(along with two related email "5 Minute Journal Clubs")

Faculty

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

↓

Patterns of Care Study 2

↓

Mailing of *Meet The Professors* audio program
(along with two related email "5 Minute Journal Clubs")

Faculty

- Ronald M Bukowski, MD
- Toni K Choueiri, MD
- Daniel J George, MD
- Robert J Motzer, MD

↓

Patterns of Care Study 3

2

Primary Topics/Objectives for Integrated Renal Cell Cancer Curriculum

1. Adjuvant therapy
- Ongoing trials
- Lack of evidence to support adjuvant therapy outside of a protocol situation

2. Management of metastatic disease
- Selection of patients to be observed expectantly without specific antitumor therapy
- Role of nephrectomy for patients presenting with metastatic disease; neoadjuvant systemic therapy
- Selection of first- and second-line therapy and sequencing strategies for systemic agents in metastatic disease

3. Management of side effects and toxicity of systemic agents: VEGF monoclonal antibodies, tyrosine kinase inhibitors (TKIs) and mTOR inhibitors
- TKIs: Indications for dose adjustment or discontinuation; evidence that "more is better"
- Tolerability and side effects of bevacizumab (with or without interferon)
- Management of complications of mTOR inhibitors (pneumonitis, infections, metabolic abnormalities)

4. Current clinical research initiatives
- Studies of combinations of biologic agents (lack of evidence to support combination biologic therapy outside of a protocol)
- Development of new agents with improved therapeutic indices, including the VEGF TKIs pazopanib and axitinib

The week after ASCO we convened a group of RCC clinical investigators, selected with input from our project co-chair, Bob Figlin, and spent a day debating the goals of the project and discussing the cases and questions posed during the US Oncology interviews. These researchers also presented cases from their practices to make important teaching points. An audio program of highlights from this fascinating event is enclosed.

One of the critical outcomes of this "Think Tank" was the development of a very specific focus for our CME interventions (Figure 2), and these important topics will be addressed in every phase of this project. To better understand the issues raised in the initial US Oncology interviews and at the Think Tank, we then launched the first of three national surveys of US-based medical oncologists.

Results from this unique assessment will be presented in a second audio program that will be mailed in about two months. This activity will use a format with which we have a lot (and I do mean a lot!) of experience, namely one-on-one interviews with investigators who are not only well versed and clinically experienced but also teachers in the highest sense — the attendings that every fellow tries to join for rounds.

Finally, in four months we will distribute our third audio program, which will feature our tried and true *Meet The Professors* tableau. For this specific edition, we have partnered with our neighbors across Alligator Alley in Southwest

Florida, the Florida Cancer Specialists group, who are cooking up some fascinating cases for a panel of investigators to discuss.

Will this endeavor be helpful to those out there on the front lines? We hope so because after decades of having not much more to offer people with advanced RCC other than supportive care and hospice, we now have many new exciting but somewhat complicated treatment options. It is critical that physicians know how to use new therapies effectively and appropriately, but also and perhaps more importantly, they must be reminded about offering participation in current research trials with important clinical endpoints and critical translational components.

These studies (Figure 3) not only present patients and physicians with the opportunity to accelerate the pace of progress, but in many cases, as with the people represented in Bob Motzer's waterfall plot, a real opportunity for patients to benefit.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
September 18, 2009

3

Select Active Phase II-III Trials in RCC

Adjuvant trials

- Phase III randomized study of adjuvant sunitinib malate versus sorafenib versus placebo in patients with resected renal cell carcinoma – First listed protocol ID: ECOG-E2805
- A clinical trial comparing efficacy and safety of sunitinib versus placebo for the treatment of patients at high risk of recurrent renal cell cancer – First listed protocol ID: A6181109
- Phase III randomized study of sorafenib tosylate in patients with resected primary renal cell carcinoma at high or intermediate risk of relapse – First listed protocol ID: MRC-RE05-SORCE

Second generation VEGF TKIs

- Extension study to VEG105192 to assess pazopanib in patients with advanced/metastatic renal cell cancer – First listed protocol ID: VEG107769
- Axitinib (AG 013736) as second-line therapy for metastatic renal cell cancer – First listed protocol ID: A4061032
- Pazopanib versus sunitinib in the treatment of locally advanced and/or metastatic renal cell carcinoma – First listed protocol ID: 108844
- Phase III randomized study of pazopanib hydrochloride in patients with refractory or relapsed metastatic soft tissue sarcoma – First listed protocol ID: EORTC-62072

Biologic combinations

- Study comparing bevacizumab + temsirolimus vs bevacizumab + interferon alfa in advanced renal cell carcinoma subjects – First listed protocol ID: 3066K1-3311
- Safety and efficacy of bevacizumab with everolimus versus interferon alfa-2a and bevacizumab in adult patients with kidney cancer – First listed protocol ID: CRAD001L2201
- Phase II study of sunitinib malate and erlotinib hydrochloride in patients with unresectable or metastatic renal cell carcinoma – First listed protocol ID: OHSU-2683

Select Excerpts from the Discussion

DR JONASCH: At this point, no adjuvant therapies have proven beneficial in renal cell carcinoma (RCC). In fact, immunotherapy has been shown conclusively not to be of benefit (Tsimafeyeu 2008).

Several clinical trials are evaluating the role of anti-angiogenic agents in the adjuvant setting, including ECOG-E2805 in the United States, evaluating sunitinib versus sorafenib versus placebo (1.1).

Protocol modifications have been necessary in the current trials because of the challenges of administering these drugs to patients in this setting. The hypothesis is that because these agents provide some benefit in the metastatic setting, they may be beneficial as adjuvant therapy, but that needs to be proven.

Absolutely no role currently exists for any of these agents in high-risk renal cell cancer outside of a protocol setting.

DR FIGLIN: With the patients I have cared for on the Intergroup study, I have found toxicity to be an issue, and the intolerance to therapy is surprising.

A patient with early disease and a chance of cure without further therapy possibly has a different set of expectations with respect to treatment than a patient with metastatic disease and no opportunity for cure. Some patients discontinue treatment because of toxicities that would have been perceived as bearable by a patient with metastatic disease.

We are not sure where the discrepancy in tolerance lies between the two disease settings. It is unlikely that patients in the adjuvant setting metabolize the drugs differently.

We have the same treatment discussions about side effects with patients in the adjuvant setting as we do with those who have metastatic disease, but their ability and desire to tolerate the side effects is different from what I would expect.

It will be interesting to see the results of these studies. It's nice that the trial includes a placebo control arm so we'll have objective data. However, pending results of the trial, I do not offer adjuvant treatment outside of a protocol setting.

DR HUTSON: Patients, particularly those with high-risk disease, commonly ask if they can receive adjuvant therapy off study. Urologists also may pose this question.

However, once the lack of data to support adjuvant treatment outside of a clinical trial is explained and patients are told that we do not recommend such treatment at this time, most patients in my experience are comfortable with either enrolling in a trial or agreeing to watchful waiting. ■

1.1

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: 1,413 (8/8/09)
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, August 2009; **www.ctsu.org**.

SELECT PUBLICATION

Tsimafeyeu IV et al. **A phase II study of GM-CSF, IFN alpha and IL-2 in adjuvant setting for high-risk renal cell carcinoma patients.** *Proc ASCO* 2008;**Abstract 16123**.

MANAGEMENT OF METASTATIC DISEASE

Selection of Systemic Therapy and Sequencing Strategies

DR ATKINS: Three different treatment approaches are now being used in kidney cancer — immunotherapy, VEGF pathway inhibition and mTOR pathway inhibition. The decision lies in what is the best first-line treatment and what is the best sequence of treatments to use for that particular patient and that particular tumor.

DR QUINN: Of the VEGF tyrosine kinase inhibitors (TKIs), sunitinib is supported by the best data (Motzer 2009; [2.1]). I might be concerned about sunitinib in patients with preexisting cardiac issues, such as a reduced ejection fraction, atrial fibrillation or prior coronary disease that now may be stable.

For a patient with impaired cardiac status, I might choose sorafenib initially because a reduction in left ventricular ejection fraction has been reported with sunitinib in a small fraction of patients.

At this time, we have not observed the same proportion of patients developing a significant reduction in ejection fraction with sorafenib,

although the two agents have not been compared directly.

I believe that the clearest indication for temsirolimus in the first-line setting is for patients considered to be at poor risk. Those of us in academic practice tend to see more of these patients, as they account for only about 15 or 20 percent of a broad renal practice.

Temsirolimus is used frequently in the second- and third-line settings, but our data are not as good in these settings, although we have some coming from the clinical trial evaluating sorafenib and temsirolimus for patients who have experienced disease progression on sunitinib.

DR HUTSON: We don't know the appropriate sequence for second- and third-line therapy. One of the goals right now is to try to enable the patient to receive all of the active drugs at some point in the treatment course. We recognize that with front-line therapy, most patients should receive VEGF-directed agents. What to switch to for second-line therapy is unclear, and that's a topic in clinical trials.

Although we have clinical trial data to suggest that if you experience a side effect from sunitinib you are at no greater risk of experiencing that side effect with sorafenib, the belief persists that that may happen. Thus, some patients don't want to attempt another VEGF inhibitor therapy.

When I enrolled patients in the pivotal everolimus trial, which was third line after the patients had already received sunitinib and sorafenib, most of them tolerated everolimus extremely well. It was somewhat like a breath of fresh air.

DR FIGLIN: Some tumors are primarily refractory to agents such as sunitinib. The randomized trial (NCT00474786) Dr Hutson is conducting, evaluating temsirolimus versus sorafenib, may provide some answers.

I've certainly had patients referred to my practice with disease that appears to be primarily refractory to a VEGF receptor TKI. I recommend almost uniformly that they proceed directly to an mTOR inhibitor.

2.1

Updated Results for Sunitinib Compared to Interferon-α (IFN-α) for Patients with Metastatic Renal Cell Carcinoma (RCC)

"This randomized phase III trial compared sunitinib with IFN-α as first-line treatment of patients with metastatic RCC. The primary end point was progression-free survival, which was met at the second interim analysis [Motzer NEJM 2007] and remained 11 months for sunitinib compared with 5 months for IFN-α in this updated follow-up. Sunitinib treatment was associated with longer survival compared with IFN-α (26.4 *v* 21.8 months, respectively).

Sunitinib demonstrates longer overall survival compared with IFN-α plus improvement in response and progression-free survival in the first-line treatment of patients with metastatic RCC. The overall survival highlights an improved prognosis in patients with RCC in the era of targeted therapy."

SOURCE: Motzer RJ et al. *J Clin Oncol* 2009;27(22):3584-90.

Expectant Observation without Antitumor Therapy

DR JONASCH: One important initial option is to delay systemic therapy and follow patients with imaging.

An example of such a patient would be an older individual, someone in his or her midseventies who received a prior nephrectomy, who now presents with relatively slow-growing bilateral pulmonary nodules, is not a candidate for IL-2 and has an excellent performance status and states clearly that quality of life is paramount. The patient is not bothered by this disease, it's clear the disease is not progressing at a rapid pace and it's not surgically resectable. This is the sort of individual with whom you can sense whether the disease is changing quickly.

DR ATKINS: One of the most common referrals I take now among patients with untreated kidney cancer is the type of patient that Eric described. The patient wants some sort of treatment, and the community oncologist isn't sure of the right time to start therapy, so the patient is referred to me. If our group says, "You can wait," the patient feels reassured about being observed. So that's a common approach that we use — to watch patients until significant disease progression leads to symptoms. Then we initiate treatment.

DR FIGLIN: I would agree with that if the patient had lung-only disease with some length of a disease-free interval, say a patient with N2 or lymph node-positive disease of modest size. However, I will not delay treatment for a patient with bone and liver disease.

DR JONASCH: It's a matter of burden and pace. If an asymptomatic patient comes in with large-volume lung metastases, would you treat that patient?

DR ATKINS: Yes, although I might check to see how quickly the metastases developed. For someone with large-volume disease that grew 20 percent and could cause symptoms, I'd start treatment.

DR MOTZER: It's difficult to reach a consensus because you can argue that if a patient walks through the door with metastatic renal cell carcinoma (mRCC), we should offer sunitinib therapy. I don't necessarily wait for another scan.

DR FIGLIN: Brian Rini and Bernard Escudier are starting a trial of immediate versus delayed sunitinib therapy for patients with defined disease parameters. If they can complete the trial, we may have an objective sense of whether late therapy initiation is appropriate compared to early initiation.

Role of Nephrectomy and Neoadjuvant Systemic Therapy

DR JONASCH: Two prospective, international trials will evaluate the role of nephrectomy for patients treated with sunitinib. The CARMENA trial is evaluating up-front nephrectomy followed by sunitinib versus no nephrectomy followed by sunitinib (2.2).

The EORTC is also about to open a trial that will compare up-front nephrectomy followed by sunitinib to three cycles of sunitinib followed

by nephrectomy in patients for whom nephrectomy is considered appropriate (2.2). The EORTC trial will also ask important questions about the interaction between preceding systemic therapy, the perioperative period and the presence or absence of nephrectomy in terms of the efficacy of sunitinib.

DR QUINN: Wood and colleagues presented a report at ASCO 2009 evaluating neoadjuvant sunitinib for patients with unresectable primary renal cell carcinoma (Wood 2009; [2.3]). The authors reported on three patients — 21 percent — who were able to undergo primary tumor resection after neoadjuvant sunitinib therapy.

Interestingly, a median of only three cycles of sunitinib were administered. We know from the first-line sunitinib study that patients who receive sunitinib continue to respond with

2.2

Ongoing and Planned Phase III Studies Integrating Nephrectomy and Sunitinib (S) for the First-Line Management of mRCC

Protocol	No. of patients	Eligibility	Randomization	Primary endpoint	Expected completion
CARMENA[1]	576	Nephrectomy-eligible, clear cell mRCC	Arm 1: Nephrectomy → S Arm 2: S	Overall survival: Equivalence	Dec. 2015
EORTC[2]	440	Clear cell mRCC	Arm 1: Nephrectomy → S Arm 2: S → nephrectomy	Progression-free survival: Superiority	Not reported

Key fundamental questions addressed:

[1] Is cytoreductive nephrectomy clinically beneficial in the treatment of mRCC with TKIs?
[2] If nephrectomy is essential, which intervention (surgical versus TKI therapy) should be performed first?

SOURCES: **www.clinicaltrials.gov**; Belmunt J. *Ann Oncol* 2009;20(Suppl 1):i13-7; Biwas S et al. *Oncologist* 2009;14(1):52-9.

2.3

Sunitinib for Patients with Unresectable Primary Renal Cell Carcinoma (RCC)

Clinical outcome (n = 18)	Sunitinib (50-mg continuous dosing, 6-week cycles)
Converted to resectable disease	37%
Primary tumor shrinkage*	72%

* All evaluable patients with clear cell histology demonstrated primary tumor shrinkage.

"Sunitinib has activity in primary RCC tumors, permitting subsequent resection in a subset of patients with initially unresectable tumors. Continued prospective evaluation is required to optimize patient selection and the timing of surgery."

SOURCE: Wood L et al. *Proc ASCO* 2009;**Abstract 5096**.

time. In fact, the partial response rate continues to climb the more we follow that study (Motzer 2009). So the optimal response may not yet have been seen.

DR LOVE: Bob, do you believe a role exists for this type of strategy outside a protocol setting, either short-term therapy as in this study or longer-term therapy?

DR FIGLIN: My own bias is that neoadjuvant treatment for patients with primary tumors intact — whether it's for locoregional or metastatic disease — should still be contemplated in an environment of a clinical research study.

DR ATKINS: I remain uncertain as to whether the concept of shrinking the tumor allows more normal tissue to be spared at surgery, so we need more information to determine whether this is even a worthwhile goal to pursue. ■

SELECT PUBLICATIONS

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.

Wood L et al. **Sunitinib in patients (pts) with unresectable primary renal cell carcinoma (RCC).** *Proc ASCO* 2009;**Abstract 5096**.

SIDE EFFECTS AND TOXICITIES OF SYSTEMIC THERAPY

VEGF Tyrosine Kinase Inhibitors

DR QUINN: When we administer a VEGF TKI to a new patient with mRCC, our goal is to keep the patient on full-dose therapy if possible. Last year we examined our practice data and found that approximately 80 percent of our patients on VEGF TKIs are still receiving full-dose therapy at six months, provided that the disease has not progressed.

When we examine the community data from some of the insurance payers, we find it's approximately 50 percent at best. Several reasons may explain this difference of 30 percent, but many community practitioners drop the dose quickly, whereas those of us with more experience prefer to manage the toxicities first. For example, if patients are hypertensive, we optimize their antihypertensive regimen, or if they have diarrhea, we administer something to intervene, while maintaining the full dose of TKI therapy.

DR HUTSON: We know from the existing data that interpatient pharmacokinetic variability is wide and that more drug exposure, as measured by AUC, produces greater efficacy with many of these drugs (Houk 2007; [3.1]).

In practice, we've tried alternative dosing strategies with selected patients, but we have no data to guide us beyond the traditional dosing schedule. A Phase II trial is under way evaluating continuous dosing at 37.5 milligrams daily versus the standard schedule of 50 milligrams daily, four weeks on, two

weeks off (Renal EFFECT trial, NCT00267748).

When I have a patient with stable disease on the 50-mg dose of sunitinib who is developing side effects severe enough to affect quality of life, I will consider dose reduction. However, when I reduce the dose, I sometimes see disease progression on a follow-up scan. I then try to change the schedule to recapture control yet keep the 50-mg dose because it seems that's what is needed. I believe something like two weeks on, one week off is reasonable for select individuals.

We don't want to resort to dose reduction or changing the schedule as our initial maneuver. I believe we need to try to manage toxicities and only use alternative dosing strategies when necessary.

DR ATKINS: Although the data suggest that more drug is better with regard to sunitinib, we're dosing based on pill size rather than body size. It's probably wrong to assume that the blood levels, which are probably most important, are the same in a 50-kg woman as in a 150-kg man receiving the same dose.

It might make sense to have more dose sizes available and to fix doses based on patient blood levels, as we do with antibiotics or anticonvulsants, because we're trying to reach a certain degree of receptor inhibition to achieve the effect.

The problem with multikinase inhibitors such as sunitinib is that in hitting some of their targets they may be contributing to the toxicity but not adding to the efficacy. The hope is that some of the newer drugs being

3.1

Probability of Partial or Complete Response Based on Mean Daily Sunitinib (SU) Exposure in Patients with Metastatic Renal Cell Carcinoma (mRCC)

"PK (pharmacokinetic) and efficacy data from 3 studies (phase II and III) of SU (25-62.5 mg/day; 4 wks dosing followed by 2 wks off) in treatment-naïve (N = 44) and cytokine-refractory mRCC pts (N = 148) were analyzed. Estimates of pt PK were used to calculate steady-state Area Under the Curve (AUCss) for SU, SU12662 [active metabolite] and TD [total drug], which were used as the exposure measure in a PKPD analysis of partial response (PR) rates, time to tumor progression (TTP), overall survival (OS), and tumor volume changes.

The probability of a PR for cytokine-refractory pts increased with increasing AUCss for SU and TD. The odds-ratio suggested a 2.6-fold increase in PR frequency for each unit increase in AUCss. Longer TTP and OS were also noted in pts with high SU and TD AUCss. In treatment-naïve pts on SU, there was very little observed tumor progression or death (only 5 pts progressed and only 1 death) limiting the ability to analyze exposure-response.

SU and TD AUCss correlated significantly with the probability of a PR in cytokine-refractory pts, and longer TTP and OS. Limited data were available for treatment-naïve pts. The tumor growth dynamics model provided a good description of tumor volume changes with SU for both populations. This exposure-response analysis indicates that increased exposure to SU is associated with clinical benefit."

SOURCE: Houk BE et al. *Proc ASCO* 2007;**Abstract 5027**.

tested, which are more selectively active against the VEGF pathways, may have less off-target toxicity and be better tolerated.

DR MOTZER: I believe it's important to stay with the evidence-based data, so I adhere to the way sunitinib was administered in the Phase III trial. In the studies, we generally dose reduce for toxicity and adhere to the four-two schedule. I expect we will have data shortly on the efficacy and toxicity of the continuous versus the four-two schedule. I understand the interest people have in deviating from the standard dose in highly selected instances, but I believe those are few and far between and that it's important to stay with the dose that you know is safe and effective.

DR HUTSON: The fatigue associated with sunitinib is challenging. It's been well described that some of these TKIs can induce hypothyroidism, so one should periodically check thyroid function studies of patients with increased fatigue and intervene with an agent such as levothyroxine when indicated.

Other possible causes of fatigue include anemia and hypoadrenalism, and renal cell carcinoma has been associated with cortisol changes. However, often it's simply the drug. I don't recommend stimulants, although many oncologists are comfortable using agents such as methylphenidate. Rather, I would consider dose interruption or reduction if the fatigue was affecting quality of life.

DR QUINN: Prophylactic treatment to prevent skin problems is important for patients receiving the VEGF TKIs. If we can, we begin skin treatments before they receive the drug, starting with lanolin-based creams. Sorafenib produces the worst hand-foot syndrome of these agents. With sunitinib, it's much more unpredictable and the presentation is a little different. Patients may be asymptomatic for eight months and then suddenly develop skin symptoms and severe pain. It's so severe that it appears to be an attack of gout, but three days after stopping the medication, they're entirely better.

DR HUTSON: When treating with sorafenib, the recommendation is to begin with the full dose for most patients. I usually see them every two weeks for the first four to six weeks to monitor toxicities.

The main side effects that require dose modification are hand-foot syndrome, gastrointestinal toxicities and hypertension. We see less fatigue with sorafenib than with sunitinib. Hand-foot syndrome can develop quickly, and we try to manage it with topical emollients. We warn patients to expect this toxicity and encourage them to use good hygiene and stay off their feet as much as possible. Some patients have a lot of callous formation and pedicures may be helpful.

For nausea or vomiting we use antiemetics, and we sometimes use proton pump inhibitors or over-the-counter acid reducers for dyspepsia. Hypertension is an early phenomenon, usually occurring within the first eight weeks, so I have my patients monitor their blood pressure daily.

One should intervene early when these patients experience side effects. If a toxicity reaches Grade III or IV, then we interrupt treatment and

three or four days after the symptoms resolve, we resume at a lower dose. Sometimes we are able to reescalate the dose down the road.

We recently reported on the long-term effects of sorafenib from the Phase III TARGET trial (Escudier 2009), and we find that after about three to four months of use, many of the main toxicities, such as diarrhea and hand-foot syndrome, become significantly less severe. So I often encourage patients to try to "tough it out" with supportive care, but we reduce the dose when necessary.

DR JONASCH: Management of diarrhea is also important with these agents. If loperamide is not effective, then we find Lomotil® helps a subset of individuals. Metamucil® with one or two ounces of water, as opposed to eight ounces of water, seems to have a positive effect on the type of diarrhea we see with sorafenib and sunitinib.

This toxicity can still be extremely problematic from a quality-of-life perspective. If this is a class effect, then I suspect we'll see it even with the more targeted TKIs. We need a better understanding of the mechanism and better treatments to help these patients.

Management of mTOR Inhibitor-Related Toxicities

DR QUINN: I believe diarrhea is a class effect with these agents. We've examined fecal fats in a number of patients, and although they don't have enough fecal fat to be in the steatorrheic range, they often have low-level nonabsorption of fat. What do we do with that information? Do we treat them with a pancreatic enzyme supplement? Do we try somatostatin or octreotide therapy? Generally, it does not become so severe that we have to do anything, but I do believe these drugs cause a low-level steatorrhea, especially when used chronically. We've created a new syndrome and now we need to determine what to do about it.

Structurally, temsirolimus and everolimus are similar, but they've never been compared head to head in treating renal cell carcinoma. Temsirolimus is administered weekly intravenously, whereas everolimus is administered orally on a daily schedule. I find that although younger patients tolerate temsirolimus, it is sometimes difficult for older patients. They develop changes such as elevated glucose, triglycerides and cholesterol, and they have more side effects. Also, after a month's administration, we often see serious mucositis and general fatigue in older patients that we tend not to see in younger patients.

Everolimus, administered daily, appears clinically to be better tolerated than temsirolimus in older patients, with regard to fatigue and their ability to cope. I have rarely had to use dose modification with everolimus, although I do sometimes if patients develop noninfective pneumonitis as a side effect of the drug. In those cases, we don't routinely stop the drug. Some of these patients are well and simply develop a mild cough. We may detect the condition on a restaging CT scan, and the addition of corticosteroids

— oral prednisone — may be sufficient to resolve it.

On the other hand, if the patient is sick and has an infiltrate in the lung, then we must stop the drug. We are aggressive with these patients. They are hospitalized, assessed by a pulmonologist and undergo a bronchoalveolar lavage. We've had a number of patients with atypical pneumonias, including one case of pneumocystis and a couple of atypical microbacterial infections.

Fungal infections are also an issue, not only in the lung but also in other areas, because the current TOR inhibitors derive from sirolimus. They're analogs, and while I don't believe the doses we administer are as immunosuppressive as sirolimus used for organ transplantation, the parallels are important.

3.2

National Patterns of Care Study with Clinical Investigators (N = 12) and Practicing Oncologists (N = 100)

Which of the following is associated with the use of the mTOR inhibitors temsirolimus and everolimus?

	Clinical investigator	Practicing oncologist
Hyperglycemia	100%	60%
Hypercholesterolemia	100%	56%
Noninfective pulmonary pneumonitis	**100%**	**39%**
Increased susceptibility to infections	92%	37%
Hypersensitivity reactions	67%	39%
Neutropenia	50%	34%
Stomatitis	83%	27%
Renal failure	67%	21%

SOURCE: Research To Practice Patterns of Care Study, July 2009.

3.3

Incidence of Pneumonitis in a Phase III Trial of Everolimus versus Placebo in Advanced Renal Cell Carcinoma

"Treatment with everolimus prolongs progression-free survival relative to placebo in patients with metastatic renal cell carcinoma that had progressed on other targeted therapies.... Non-infectious pneumonitis, a potentially serious adverse event associated with rapamycin and rapamycin derivative treatment, is also seen with everolimus. It comprises one of a number of typical radiographic appearances with or without signs and symptoms (pleural effusion, hypoxia, cough, dyspnoea, malaise) in the absence of a non-drug cause.

Clinical evidence of grade 3 pneumonitis was reported for eight (3%) patients receiving everolimus in the current trial. A detailed analysis is planned of the radiological and clinical findings associated with lung symptoms and pneumonitis. This will provide guidance for improved diagnosis, management and, if possible, prevention of this toxicity."

SOURCE: Motzer RJ et al. *Lancet* 2008;372(9637):449-56.

These unusual infections are not that common. I would estimate that they occur in less than five percent of patients, but the community oncologist who's treating a few of these patients needs to be aware and be aggressive in evaluating them when they become ill.

DR MOTZER: The mTOR inhibitor-related toxicity that oncologists need to be aware of is noninfectious pneumonitis (3.2).

In the everolimus pivotal study, approximately 14 percent of patients developed this condition (Motzer 2008; [3.3]). The protocol stipulated that if the pneumonitis was Grade II, treatment must be interrupted. Therapy was restarted if it then improved to Grade I or less.

With Grade III pneumonitis, which generally means symptoms that interfere with activities of daily living, such as those requiring oxygen, the inhibitor was stopped and the dose reduced.

Of the 30-plus patients who developed pneumonitis on the trial, approximately half were treated with corticosteroids and I believe only six patients had to have treatment discontinued. ■

SELECT PUBLICATIONS

Bellmunt J et al. **Temsirolimus safety profile and management of toxic effects in patients with advanced renal cell carcinoma and poor prognostic features.** *Ann Oncol* 2008;19(8):1387-92.

Escudier B et al. **Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial.** *J Clin Oncol* 2009;27(20):3312-8.

Houk BE et al. **Exposure-response of sunitinib in metastatic renal cell carcinoma (mRCC): A population pharmacokinetic/pharmacodynamic (PKPD) approach.** *Proc ASCO* 2007;**Abstract 5027**.

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

CURRENT CLINICAL RESEARCH INITIATIVES

Combining Biologic Agents

DR FIGLIN: Although I believe that the idea of combining vertical or horizontal inhibition is worthy of scrutiny, it's difficult to combine vertical inhibitors that specifically target VEGF ligand and VEGF receptor because they cause synergistic toxicities.

Some of the best combinations seem to be VEGF ligand and mTOR inhibition, with which we can administer almost full doses of both drugs in sequences that are comparable to how the drugs would be administered as single agents. The Phase I trial evaluating oral everolimus combined with sunitinib was reported at ASCO (Kroog 2009), and published trials have evaluated the combination of bevacizumab and mTOR inhibition. I caution physicians that although these regimens are being evaluated in clinical trials, they

are not, in my opinion, ready for use in clinical practice.

DR ATKINS: One of the reasons for the interest in developing TKIs that are more selective in their targets is that they may be orally administered equivalents to bevacizumab and may be better combined with a TOR inhibitor or another non-VEGF pathway-blocking agent. My hope is that pazopanib and axitinib will be more direct inhibitors of a key target and more combinable.

Novel VEGF Tyrosine Kinase Inhibitors

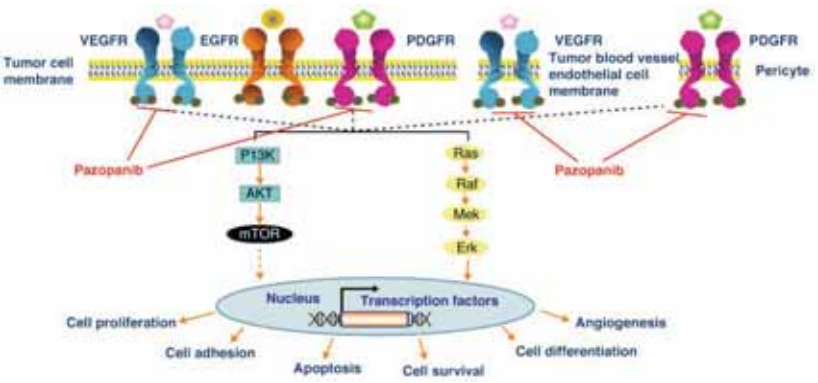
DR FIGLIN: We are now evaluating second- or third-generation agents targeting the VEGF pathway, trying to find drugs that will target that pathway with equal or superior efficacy but less off-target toxicity. One agent under study is pazopanib, an oral anti-angiogenic inhibitor that targets PDGFR and c-Kit, but most importantly it has nanomolar inhibitory concentrations against VEGF receptors 1, 2 and 3 (4.1).

DR HUTSON: We used a randomized discontinuation design for a Phase II trial of pazopanib for patients with metastatic renal cell carcinoma. After a 12-week run-in period with pazopanib, response was assessed using CT scans. The patients who demonstrated complete or partial responses continued receiving open-label pazopanib, those with progressive disease were taken off study and the patients with stable disease were randomly assigned to receive either pazopanib or placebo.

After the first 60 patients were enrolled, a planned interim analysis revealed a partial response rate of 27 percent. Based on this robust level of activity, the randomization was discontinued and all patients crossed over to pazopanib. The study continued as an open-label, single-arm study.

4.1

Pazopanib: Mechanisms of Action



SOURCE: With permission from Sonpavde G et al. *Expert Opin Investig Drugs* 2008;17(2):253-61.

The final efficacy analysis revealed a complete response in three patients, a partial response in 33 percent of the patients and a stable disease rate of 45 percent, yielding a clinical benefit rate of slightly more than 80 percent (Hutson 2008). Progression-free survival was 11.9 months, and the duration of response was 68 weeks.

The toxicities included hypertension, liver transaminase elevation, diarrhea and hair and skin depigmentation. The rates of fatigue and hand-foot syndrome were much lower than those recorded with similarly targeted agents such as sorafenib and sunitinib. Overall, the rate of Grade III or IV toxicities was low, occurring in two percent of patients or less.

DR FIGLIN: In a Phase III trial comparing pazopanib to placebo for patients with advanced disease (VEG105192), the progression-free survival was more than doubled with pazopanib — 4.2 months on the placebo arm versus 9.2 months on the treatment arm — and the quality-of-life data demonstrated no difference between the two groups (Sternberg 2009; [4.2, 4.3]).

In a subsequent extension of the open-label portion, patients who received the placebo could cross over to pazopanib. This trial demonstrated similar benefits with respect to objective response and progression-free survival and a similar spectrum of side effects (Hawkins 2009; [4.4]). It was clear that the crossover allowed those patients to be recaptured with a VEGF TKI response.

DR HUTSON: It appears that pazopanib is in the same efficacy ballpark as sunitinib, based on progression-free survival and response rate data.

In addition, clinical trial data demonstrate that some of the toxicities that make the use of sunitinib difficult

4.2

VEG105192: A Phase III Trial Comparing Pazopanib to Placebo as Front-Line Therapy for Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma: Efficacy Data

	Pazopanib (n = 290)	Placebo (n = 145)	Hazard ratio
Median progression-free survival	9.2mo	4.2mo	0.46[1]
Treatment naïve (n = 233)	11.1mo	2.8mo	0.40[1]
Cytokine pretreated (n = 202)	7.4mo	4.2mo	0.54[2]
Median overall survival	21.1mo	18.7mo*	0.73[3]
Overall response rate (ORR, CR + PR)	30%	3%	—
Treatment naïve	32%	4%	—
Cytokine pretreated	29%	3%	—
Duration of response	59wk	—	—

[1] $p < 0.0000001$; [2] $p < 0.001$; [3] $p < 0.02$; * 48% of patients received pazopanib after disease progression.

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

— fatigue, diarrhea, mucositis and hand-foot syndrome — appear to be uniquely decreased with pazopanib (Hawkins 2009; [4.4]). In my view, pazopanib may be more tolerable than sunitinib with long-term use.

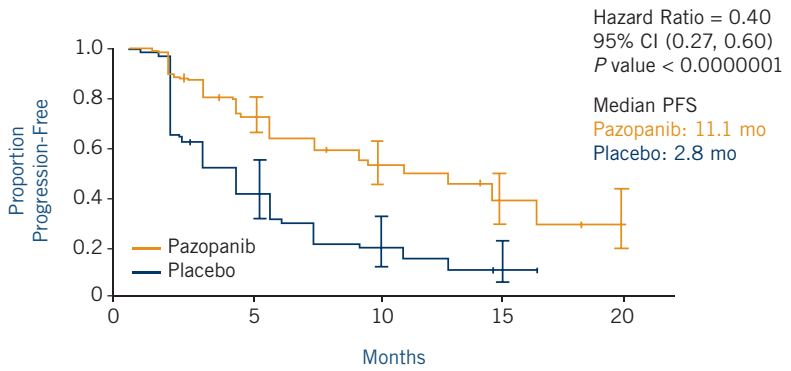
DR MOTZER: The ongoing head-to-head study comparing pazopanib to sunitinib is critical in terms of evaluating adverse events and the efficacy of these two agents (NCT00720941).

DR QUINN: Axitinib is probably one of our more potent VEGFR-2 inhibitors. Data from the Phase II trials of axitinib demonstrate a significant partial response rate that is at least equivalent to those with sunitinib and pazopanib and may be better than what we see with sorafenib. A Phase III study of second-line axitinib versus sorafenib for metastatic renal cell cancer, known as the AXIS trial, is ongoing.

DR HUTSON: Oliver Rixie presented data examining the efficacy of axitinib, AUC levels and blood pressure. A pharmacokinetic analysis

4.3

VEG105192: Progression-Free Survival in the Treatment-Naïve Subpopulation



SOURCE: With permission from Sternberg CN et al. ASCO 2009;**Abstract 5021**.

4.4

Open-Label Extension Study of Pazopanib for Patients with Advanced Renal Cell Carcinoma: Treatment-Related Toxicity (Any Grade, N = 69)

Hypertension	41%	Hair color changes	38%
Diarrhea	35%	Nausea	21%
Anorexia	18%	ATL increase	14%
Fatigue	14%	Proteinuria	13%
AST increase	11%	Vomiting	11%

SOURCE: Hawkins RE et al. *Proc ASCO* 2009;**Abstract 5110**.

confirmed that higher AUC levels were associated with greater efficacy and served as an independent marker of efficacy (Rixie 2009; [4.5]).

In addition, elevated diastolic blood pressure was an independent marker and a strong predictor of clinical efficacy. However, no correlation was apparent between the AUC and maximum diastolic blood pressure. I would have expected that if hypertension were truly an on-target toxicity, the higher AUC levels and higher blood pressure would be related to each other. ■

4.5

Diastolic Blood Pressure (dBP) and Pharmacokinetics as Predictors of Axitinib Efficacy in mRCC

Analysis of two multiple-dose Phase II studies in patients with cytokine- or sorafenib-refractory mRCC (N = 114)

Parameter	Median overall survival
dBP ≥ 90mmHg	130 weeks
dBP < 90mmHg	42 weeks
AUCss ≥ median	88 weeks
AUCss < median	69 weeks
Increased axitinib exposure (AUC) and dBP ≥ 90 mmHg were independently associated with longer overall survival	
dBP ≥ 90 mmHg, AUCss < median	120 weeks
dBP ≥ 90 mmHg, AUCss ≥ median	131 weeks
dBP < 90 mmHg, AUCss < median	42 weeks
dBP < 90 mmHg, AUCss ≥ median	43 weeks
dBP ≥ 90 mmHg during axitinib therapy is associated with clinical efficacy in patients with mRCC and is not a reflection of axitinib drug levels	

AUCss = area under the concentration-time curve at steady-state

SOURCE: Rixie O et al. *Proc ASCO* 2009;**Abstract 5045**.

SELECT PUBLICATIONS

Hawkins RE et al. **An open-label extension study to evaluate safety and efficacy of pazopanib in patients with advanced renal cell carcinoma (RCC).** *Proc ASCO* 2009;**Abstract 5110**.

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

Kroog GS et al. **Phase I trial of RAD001 (everolimus) plus sunitinib in patients with metastatic renal cell carcinoma.** *Proc ASCO* 2009;**Abstract 5037**.

Rixie O et al. **Diastolic blood pressure (dBP) and pharmacokinetics (PK) as predictors of axitinib efficacy in metastatic renal cell cancer (mRCC).** *Proc ASCO* 2009;**Abstract 5045**.

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**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A large Phase III trial of sunitinib versus interferon-α for patients with previously untreated metastatic renal cell carcinoma demonstrated significant improvement in _____ among patients treated with sunitinib.**
   a. Overall survival
   b. Progression-free survival
   c. Both a and b

2. **The randomized placebo-controlled adjuvant Phase III ECOG-E2805 trial is evaluating _____ versus _____ for patients with resected renal cell carcinoma.**
   a. Bevacizumab; interferon
   b. Bevacizumab; erlotinib
   c. Sunitinib; sorafenib
   d. Axitinib; sorafenib

3. **The NCT00474786 trial led by Dr Hutson is evaluating sorafenib and temsirolimus as second-line therapy for patients with advanced renal cell carcinoma for whom first-line therapy with sunitinib has failed.**
   a. True
   b. False

4. **Wood and colleagues presented a report at ASCO 2009 evaluating neoadjuvant _____ for patients with unresectable primary renal cell carcinoma.**
   a. Sorafenib
   b. Sunitinib
   c. Temsirolimus

5. **In the first-line treatment of metastatic renal cell carcinoma, the standard dose of sunitinib is _____.**
   a. 50 milligrams daily, four weeks on, two weeks off
   b. 37.5 milligrams daily, four weeks on, two weeks off
   c. 50 milligrams daily, continuous
   d. 37.5 milligrams daily, continuous

6. **Noninfectious pneumonitis, a potentially serious adverse event, has been reported in association with _____ therapy.**
   a. Axitinib
   b. Everolimus
   c. Sunitinib
   d. Sorafenib

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

8. **Pazopanib is an oral anti-angiogenic inhibitor that targets which of the following?**
   a. PDGFR
   b. c-Kit
   c. VEGFR-1
   d. VEGFR-2
   e. VEGFR-3
   f. All of the above

9. **Rixie and colleagues published data from a clinical trial of axitinib for metastatic renal cell carcinoma demonstrating that higher AUC levels were associated with greater efficacy and served as an independent marker of efficacy.**
   a. True
   b. False

10. **Houk and colleagues published pharmacokinetic/pharmacodynamic data on sunitinib for the treatment of metastatic renal cell carcinoma showing that total drug AUCs correlated significantly with which of the following?**
    a. Probability of response
    b. Time to tumor progression
    c. Overall survival
    d. All of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Renal Cell Cancer Update — Think Tank Issue 1, 2009

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

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

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

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

	BEFORE	AFTER
Ongoing adjuvant trials in RCC	4 3 2 1	4 3 2 1
Side effects and tolerability of multikinase inhibitors, VEGF monoclonal antibody therapy and mTOR inhibitors in advanced RCC	4 3 2 1	4 3 2 1
Clinical strategies for managing treatment-related toxicity in patients with advanced RCC	4 3 2 1	4 3 2 1
Indications for dose adjustment or discontinuation of multikinase inhibitors and the potential effect on treatment efficacy	4 3 2 1	4 3 2 1
Clinical strategies for sequencing treatments for advanced RCC	4 3 2 1	4 3 2 1
Efficacy and safety of the oral multikinase angiogenesis inhibitor pazopanib for patients with treatment-naïve or cytokine-pretreated advanced clear cell RCC	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:

- Evaluate the role of nephrectomy for patients presenting with metastatic RCC. . . 4 3 2 1 N/M N/A
- Identify patients with RCC who may benefit from expectant observation, and consider factors affecting the timing of initial treatment . . . . . 4 3 2 1 N/M N/A
- Apply the results of existing and emerging clinical research to the evidence-based selection of front-line and subsequent therapy for metastatic RCC . . . . . 4 3 2 1 N/M N/A
- Compare and contrast the safety and tolerability of cytokine immunotherapy, multikinase inhibitors, mTOR inhibitors and VEGF monoclonal antibody therapy for RCC . . . . . 4 3 2 1 N/M N/A
- Recommend supportive management strategies to effectively address the side effects of targeted treatments for RCC . . . . . 4 3 2 1 N/M N/A
- Recognize indications for dose adjustment or discontinuation of multikinase inhibitor therapy, and assess the effect of both on ultimate treatment efficacy. . . 4 3 2 1 N/M N/A
- Recall the scientific rationale for and early efficacy of novel investigational compounds demonstrating activity in RCC. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with RCC about the availability of ongoing clinical trial participation. . . . . 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 moderator for this educational activity

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

Faculty	Knowledge of subject matter				Effectiveness as an educator			
Michael B Atkins, MD	4	3	2	1	4	3	2	1
Robert A Figlin, MD	4	3	2	1	4	3	2	1
Thomas E Hutson, DO, PharmD	4	3	2	1	4	3	2	1
Eric Jonasch, MD	4	3	2	1	4	3	2	1
Robert J Motzer, MD	4	3	2	1	4	3	2	1
David I Quinn, MBBS, PhD	4	3	2	1	4	3	2	1
Moderator	**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 moderator for this activity:

.....

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Renal Cell Cancer™

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U P D A T E

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