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Renal Cell Cancer™

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

INTERVIEWS

Robert A Figlin, MD

Gary R Hudes, MD

Ronald M Bukowski, MD

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Renal Cell Cancer Update

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OVERVIEW OF ACTIVITY

Due to an increased understanding of the biology of renal cell cancer (RCC) and emerging clinical trial data, new therapeutic options are available for patients. To assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date management strategies for RCC, this activity features expert perspectives on how the latest research developments apply to current clinical practice.

LEARNING OBJECTIVES

- Apply an understanding of the biology of clear cell RCC, including inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene and the pathway leading to VEGF overexpression, to therapeutic decision-making.
- Develop management strategies for advanced RCC, considering the safety and efficacy profiles of targeted biologic therapies inhibiting VEGF, PDGF and EGF receptors.
- Review clinical efficacy and safety data for inhibitors of the mammalian target of rapamycin (mTOR), and develop a plan for incorporating these agents into treatment plans for advanced RCC.
- Evaluate emerging data on the safety and efficacy of combining targeted therapies for patients with RCC, and apply this information to clinical practice.
- Devise treatment plans for patients with RCC, considering molecular targets and the pathologic grade of the tumor.
- Develop an approach for the sequencing and duration of treatment with targeted biologic therapies.
- Counsel appropriately selected patients with RCC about potential participation in ongoing clinical trials in the adjuvant and metastatic settings.

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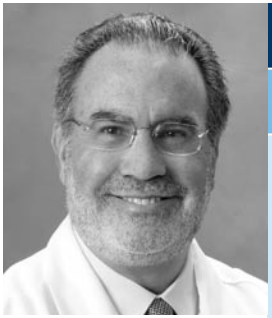
RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.



INTERVIEW

Robert A Figlin, MD

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

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Track 1

DR LOVE: Can you comment on the survival data from the trial of sunitinib versus interferon as first-line therapy for mRCC?

DR FIGLIN: This is the trial that has changed the standard treatment for kidney cancer. The study enrolled 750 patients and compared sunitinib to interferon.

It demonstrated more than a twofold prolongation in progression-free survival, and the objective response rate, both complete and partial, was almost 40 percent with sunitinib (Motzer 2007). Approximately 80 percent of patients experienced disease control, and in January 2006 sunitinib was approved for the treatment of mRCC.

At ASCO in 2008 I presented the survival analysis, which showed that survival for the patients treated with sunitinib was 26.4 months compared to approximately 21 months in the control group (Figlin 2008; [1.1]).

The median survival for patients with metastatic kidney cancer in the interferon era was approximately 13 months, and this trial was designed to improve survival by 37.5 percent, increasing it to 17 months.

One might ask why the control group had a survival of 21 months, which is eight months better than the historical group. When the progression-free survival benefit was realized, it was no longer ethical to not offer sunitinib to the patients on the control arm, so in 2006 patients whose disease progressed on interferon could switch to sunitinib.

DR LOVE: How did the data compare when you eliminated the patients who switched from interferon to sunitinib?

DR FIGLIN: When we analyzed the data for patients who only received sunitinib compared to those who only received interferon, the survival was 28 versus 14 months, respectively.

It's difficult to measure survival when paradigm shifts are taking place. One third of the patients treated with interferon had received sunitinib at some time, either on or off study, and 59 percent received some poststudy treatment, such as sunitinib, sorafenib, mTOR inhibitors, cytokines or chemotherapy.

Nonetheless, my conclusions are straightforward, which are that these data are the first clear and unequivocal demonstration of a survival benefit for patients with mRCC compared to our historical groups.

For those of us who have been treating kidney cancer for decades, this is the first time we can see patients living for more than two years with metastatic disease.

Approximately 80 percent of the patients will have some reduction in their tumor, in the absence of progression, during the course of their treatment with sunitinib (Motzer 2007). Thus, when patients ask me what the likelihood is that they will benefit from sunitinib, I tell them that they have an eight-in-10 chance.

DR LOVE: Do you feel that patients with mRCC are now living longer?

DR FIGLIN: Yes, our practices are growing because patients are living longer and they're coming back more frequently because they are staying on treatment longer. With a median survival of two years, some patients are living

significantly longer. I have a patient who participated in the original Phase II trial and is still on sunitinib four and a half years later — her disease is under control, and she's leading a great life.

DR LOVE: Is she in complete clinical remission?

DR FIGLIN: No, she must be maintained on the drug. If we cut back, the tumor grows. That's important for practicing oncologists to understand. These responses and this benefit are what we would characterize as maintained remissions, not unmaintained remissions. The patients must continue on these drugs, otherwise the tumor will start to grow again.

DR LOVE: With this particular patient, what toxicities has she had to deal with during the past four and a half years?

DR FIGLIN: Her major toxicity has been fatigue, followed by hand-foot syndrome. She's receiving 37.5 milligrams rather than the full 50 milligrams because of these side effects, and at that dose she's able to maintain an active and full life.

1.1

Sunitinib versus Interferon (IFN) in Previously Untreated mRCC: Efficacy Data

All patients	Sunitinib (n = 375)	IFN (n = 375)	*p*-value (log rank)
Median progression-free survival			<0.000001
Independent review	11 months	5 months	
Investigator	11 months	5 months	
Objective response			<0.000001
Independent review	39%	8%	
Investigator	47%	12%	
Median overall survival	26.4 months	21.8 months	0.051
Patients who received no poststudy treatment	**Sunitinib (n = 193)**	**IFN (n = 162)**	***p*-value (log rank)**
Overall survival	28.1 months	14.1 months	0.0033

SOURCE: Figlin RA et al. *Proc ASCO* 2008;**Abstract 5024**.

Track 9

DR LOVE: You participated in the study that evaluated sorafenib in older patients with advanced renal cell carcinoma. What did that trial show, and what is your approach in practice?

DR FIGLIN: We found no apparent difficulty administering sorafenib to patients older than age 65 compared to the population of patients who are younger than age 65 (Bukowski 2008; [3.1, page 14]).

In my practice, when I discuss sorafenib versus sunitinib with an elderly, asymptomatic patient, I explain that with one therapy, we may have to sacrifice benefit a bit, but a better quality-of-life component exists. Some patients want the more effective therapy, regardless of the toxicity, whereas others want a good quality of life and know that the other therapy will be available later if they need it.

DR LOVE: Which is better tolerated by older patients, sorafenib or sunitinib (1.2)?

DR FIGLIN: In my experience, sorafenib is better tolerated by older patients. We see less fatigue, hand-foot syndrome and hypertension in our patients who are treated with sorafenib.

1.2 **Most Common Adverse Reactions with Sunitinib and Sorafenib**

	Sorafenib 400 mg BID		Sunitinib 50 mg qd	
Adverse reaction	All grades	Grade III/IV	All grades	Grade III/IV
Systemic				
Fatigue	37%	5%	58%	7%
Cardiac				
Hypertension	17%	4%	24%	8%
Gastrointestinal				
Diarrhea	43%	2%	53%	5%
Nausea	23%	<1%	44%	3%
Vomiting	16%	<1%	24%	4%
Anorexia	16%	<1%	28%	1%
Abdominal pain	11%	2%	22%	3%
Cutaneous				
Rash	40%	<1%	19%	2%
Hand-foot syndrome	30%	6%	20%	5%
Alopecia	27%	<1%	—	—
Mucositis/stomatitis	21%	6%	45%	3%
Laboratory				
Neutropenia	18%	5%	72%	12%
Hypophosphatemia	45%	13%	36%	5%
Elevated lipase	41%	12%	52%	16%
Lymphopenia	23%	13%	60%	12%
Anemia	44%	2%	71%	4%
Thrombocytopenia	12%	1%	65%	8%
↑creatinine	—	—	66%	1%

SOURCE: Bhojani N et al. *Eur Urol* 2008;53:917-30. **Abstract**

Track 12

DR LOVE: What do you consider the optimal treatment for patients with clear cell mRCC in the front-line setting?

DR FIGLIN: Level I evidence tells us that the treatment of choice is sunitinib. Level I evidence also exists for the combination of bevacizumab and interferon in the untreated patient population.

DR LOVE: What about bevacizumab alone for these patients?

DR FIGLIN: Bevacizumab monotherapy has never been tested in Phase III trials. However, many people believe that interferon doesn't contribute much to the combination. Consider another observation published by Bernard Escudier with regard to the combination (Melichar 2008). He presented data comparing progression-free survival among patients who had received full doses of interferon versus reduced doses.

Much to our surprise, patients who received the lower doses had a longer progression-free survival, so we don't know whether the dose of interferon used when combined with bevacizumab needs to be that high. We may need to revisit the question of whether lower-dose interferon may be equally effective or possibly even more effective.

DR LOVE: What did the clinical trial of bevacizumab with or without erlotinib show?

DR FIGLIN: This was a randomized, Phase II study in mRCC, and it indicated that the addition of erlotinib did not provide additional clinical benefit. It also showed that bevacizumab monotherapy had a response rate that is lower and a progression-free survival rate that appears inferior to what we expect with the combination of bevacizumab and interferon, at least when compared study to study (Bukowski 2007; [1.3]).

1.3

Randomized Phase II Study of Bevacizumab with or without Erlotinib for Previously Untreated mRCC

Parameter	Bevacizumab + placebo (n = 53)	Bevacizumab + erlotinib (n = 50)
Overall response rate	13%	14%
Median progression-free survival	8.5 months	9.9 months
12-month progression-free survival	40%	45%
12-month survival*	83%	70%

* Analysis of second-line therapies as a possible explanation for the apparent separation of the curves revealed that 32 percent of patients had recorded receiving second-line therapy in the bevacizumab arm versus 14 percent in the bevacizumab/erlotinib arm. It is unknown whether these therapies included sorafenib or sunitinib.

SOURCE: Bukowski RM et al. *J Clin Oncol* 2007;25(29):4536-41. **Abstract**

Track 14

DR LOVE: What is your current management algorithm for patients with mRCC?

DR FIGLIN: My paradigm is simple. If a patient has a carcinoma with predominantly clear cell features, whether the prognosis is good, intermediate or poor, my treatment of choice is sunitinib.

Temsirolimus is another option for the untreated patient. This agent is now commercially available for patients with poor prognostic features, such as a lower hemoglobin level, poorer performance status, multiple sites of metastatic disease or high-corrected calcium. In my practice, if a patient has other features that worsen the prognosis, I use temsirolimus.

DR LOVE: What do you use for patients with nonclear cell histologies?

DR FIGLIN: The temsirolimus trial with untreated patients included nonclear cell histologies (Hudes 2007). In that patient population, even though sunitinib is available, one has to consider temsirolimus.

Track 18

DR LOVE: Are you participating in the Intergroup adjuvant trial (ECOG-E2805) evaluating sorafenib versus sunitinib versus placebo?

DR FIGLIN: At the City of Hope, we have entered many patients on this spectacular trial. Already more than 800 patients are enrolled, with a target accrual of 1,300. This is an interesting trial because treating a patient with these targeted therapies in the adjuvant setting is different than in the metastatic setting. Patients receiving adjuvant therapy have different expectations, and their tolerance for toxicity is different.

DR LOVE: Have you used either of these agents as adjuvant therapy outside of a clinical trial?

DR FIGLIN: I have not done so, and I will not do so. First we need to learn whether these targeted agents work in the adjuvant setting. Theoretically, the adjuvant setting includes patients with micrometastatic disease, and we have not yet determined the role of anti-angiogenesis in micrometastatic disease. It could be that angiogenesis isn't as robust and, as such, can't be inhibited as well in that micrometastatic setting. ■

SELECT PUBLICATIONS

Bukowski RM et al. **Safety and efficacy of sorafenib in elderly patients (pts) >65 years: A subset analysis from the Advanced Renal Cell Carcinoma Sorafenib (ARCCS) Expanded Access Program in North America.** *Proc ASCO* 2008;**Abstract 5045**.

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

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

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

Melichar B et al. **First-line bevacizumab combined with reduced dose interferon-{alpha} 2a is active in patients with metastatic renal cell carcinoma.** *Ann Oncol* 2008;19(8):1470-6. **Abstract**

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

INTERVIEW

Gary R Hudes, MD

Dr Hudes is Director of the Genitourinary Malignancies Program in the Department of Medical Oncology at Fox Chase Cancer Center in Philadelphia, Pennsylvania.

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Track 20 Limitations of RECIST criteria to predict survival benefit with biologic agents

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What was reported at this year's ASCO meeting related to RCC that doctors in practice need to know about?

DR HUDES: One important advance presented at this year's ASCO meeting was a trial conducted specifically for the patient who has experienced disease

progression on sorafenib or sunitinib, the two approved vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors.

What to do in the second line has been a conundrum. We've been moving from one approved drug to the next to the next, without conclusive data on what we're accomplishing. In medicine we sometimes operate without data because we have to do the best we can for the patient. It was refreshing at this year's ASCO meeting to hear of a trial that evaluated a drug — RAD001, also called everolimus — to find out how it would perform in the second-line setting (Motzer 2008).

DR LOVE: What do we know about RAD001 as opposed to temsirolimus?

DR HUDES: RAD001 is, like temsirolimus, an inhibitor of a mammalian target of rapamycin — mTOR for short. This is an interesting target in kidney cancer. It seems to control proliferation and angiogenesis. Four mTOR inhibitors are now in existence. The parent drug, rapamycin, is only used for prophylaxis of renal allograft rejection because of its immunosuppressive properties. Temsirolimus, everolimus and another drug, deforolimus, are all what we call rapalogs, or analogs of sirolimus or rapamycin.

Two of these agents have been tested in renal cancer. Temsirolimus, which was evaluated in the global ARCC study, is approved for kidney cancer. The ARCC trial was designed for patients with multiple adverse risk factors for short survival and showed a survival advantage with temsirolimus (Hudes 2007).

Later, the everolimus trial evaluated a different population — patients who had already received sunitinib or sorafenib. Patients were randomly assigned to treatment with everolimus or placebo, both with best supportive care. The study allowed a crossover to everolimus for patients who experienced disease progression on placebo.

They saw a striking benefit from everolimus compared to placebo. The median progression-free survival was four months for everolimus and 1.9 months for placebo (Motzer 2008; [2.1]).

The activity of everolimus is not surprising. The fact that patients on placebo experienced disease progression in only 1.9 months, on one hand, is perhaps a little faster than we thought. On the other hand, we had data from an older randomized discontinuation study that showed that patients experienced

2.1

Progression-Free Survival (PFS) with Everolimus versus Placebo as Second-Line Therapy for mRCC

	RAD001	Placebo	HR (95% CI)	*p*-value
Median PFS	4.0 months	1.9 months	0.30 (0.22-0.40)	<0.0001
Six-month PFS	26%	2%	—	—

SOURCE: Motzer RJ et al. *Proc ASCO* 2008;**Abstract LBA5026**.

disease progression quickly, in approximately two months, when they stopped sorafenib (Ratain 2004). So maybe these findings aren't surprising after all.

DR LOVE: What about response rates?

DR HUDES: The response rate was low — about one percent for everolimus and the same for placebo. The benefit is in stabilization of disease.

DR LOVE: When you view the data, do you believe there's something there? Two months doesn't sound like much.

DR HUDES: Yes — this is not a major lengthening of disease control, but it does establish efficacy in terms of the median effect. Some patients on that survival curve fare considerably better with disease control. As with a lot of therapies, what we accomplish is incremental.

Track 3

DR LOVE: What about clinical issues with temsirolimus versus everolimus?

DR HUDES: The mTOR inhibitors are more alike than they are different. The mechanism is specific for the mTOR protein kinase. Some differences exist in formulation. Temsirolimus is only in an IV formulation now, whereas everolimus is only in an oral formulation. In terms of the actual activity, however, it would be difficult to prove that one is better than the other.

DR LOVE: What about side effects and toxicity?

DR HUDES: Quite similar. Stomatitis is probably the most common side effect. Some fatigue, anemia, rash and diarrhea occur — after stomatitis, these are the most common toxicities. Pulmonary toxicity, which can occur in a few patients — approximately eight percent in the everolimus study — can require dose modification or temporary halting of treatment.

DR LOVE: The specific pulmonary syndrome is interstitial pneumonitis.

DR HUDES: Yes. It can be anything from ground glass infiltrates in an asymptomatic patient, which is most common, to symptomatic dyspnea with bilateral infiltrates, which require halting the treatment and treating with steroids. It's almost always reversible, however.

DR LOVE: How do you generally utilize these agents?

DR HUDES: For the patients with poor prognoses, I use temsirolimus in the first line. I also consider it as second-line therapy for patients who have experienced disease progression on sunitinib. For some patients, oral therapy is still preferable. For some of these patients, I use sorafenib as second-line therapy.

So many new agents are being tested now in kidney cancer that a practicing oncologist probably doesn't have to look far for a second-line or even a third-line trial of a new tyrosine kinase inhibitor.

Track 10

DR LOVE: Can you discuss what we know about combined biologic therapy?

DR HUDES: Combination therapy should be examined carefully. The BeST trial (ECOG-E2804) is comparing single-agent bevacizumab to three combinations: temsirolimus/bevacizumab, sorafenib/bevacizumab and temsirolimus/sorafenib. At the time that this study was designed, the sunitinib combination data were nonexistent.

A study of sunitinib/bevacizumab was presented at ASCO by the group at Memorial Sloan-Kettering (Feldman 2008). Apropos to the need for safety data before proceeding, an unacceptable rate of microangiopathic thrombocytopenia and hemolytic syndrome occurred with long-term sunitinib/bevacizumab therapy.

It was not an anticipated toxicity. Microangiopathic syndrome is not common, but it is seen occasionally with single-agent bevacizumab (Eremina 2008; [2.2]).

DR LOVE: What is the mechanism for this toxicity?

DR HUDES: Direct damage to the endothelial cell, apparently affecting the kidney. That's one explanation for the occasional decline in renal function.

DR LOVE: Did they have enough data to evaluate efficacy in the sunitinib/bevacizumab trial?

DR HUDES: They did, and it wasn't immediately clear that the response rate or duration of response was better than you would expect with single-agent sunitinib.

The BeST study (2.3) is an important trial in terms of showing that combinations are feasible. Where do you set the bar for combination therapy to justify the anticipated extra toxicity of two drugs versus one drug? The alternative way of using multiple agents — in sequence — should be explored also. ■

2.2 VEGF Inhibition and Renal Thrombotic Microangiopathy

"The glomerular microvasculature is particularly susceptible to injury in thrombotic microangiopathy, but the mechanisms by which this occurs are unclear...

To show that local reduction of VEGF within the kidney is sufficient to trigger the pathogenesis of thrombotic microangiopathy, we used conditional gene targeting to delete VEGF from renal podocytes in adult mice; this resulted in a profound thrombotic glomerular injury. These observations provide evidence that glomerular injury in patients who are treated with bevacizumab is probably due to direct targeting of VEGF by antiangiogenic therapy."

SOURCE: Eremina V et al. *N Engl J Med* 2008;358(11):1129-36. **Abstract**

2.3 BeST Trial: A Randomized Phase II Study of VEGF, RAF Kinase and mTOR Combination Targeted Therapy with Bevacizumab, Sorafenib and Temsirolimus in Advanced Renal Cell Carcinoma

Protocol ID: ECOG-E2804
Target Accrual: 360
Study Start: September 2007 Estimated Completion: September 2008

Eligibility

- Histologically confirmed, measurable metastatic clear cell renal cell carcinoma
- No history or clinical evidence of CNS disease, including primary brain tumor or brain metastases
- No history of bleeding diathesis or coagulopathy
- No clinically significant cardiovascular disease, including any of the following:
  Uncontrolled hypertension
  - Blood pressure must be ≤150/100 mm Hg on a stable antihypertensive regimen
  - Myocardial infarction or unstable angina within the past six months
  - New York Heart Association class II-IV congestive heart failure
  - Serious cardiac arrhythmia requiring medication
  - Unstable angina pectoris
  - Peripheral vascular disease ≥Grade II
- No serious, nonhealing wound, ulcer or bone fracture

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, July 2008.

SELECT PUBLICATIONS

Eremina V et al. **VEGF inhibition and renal thrombotic microangiopathy.** *N Engl J Med* 2008;358(11):1129-36. **Abstract**

Feldman DR et al. **Phase I trial of bevacizumab plus sunitinib in patients with metastatic renal cell carcinoma.** *Proc ASCO* 2008;**Abstract 5100**.

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

Motzer RJ et al. **RAD001 vs placebo in patients with metastatic renal cell carcinoma (RCC) after progression on VEGFr-TKI therapy: Results from a randomized, double-blind, multicenter phase-III study.** *Proc ASCO* 2008;**Abstract LBA5026**.

Ratain MJ et al. **Preliminary antitumor activity of BAY 43-9006 in metastatic renal cell carcinoma and other advanced refractory solid tumors in a phase II randomized discontinuation trial (RDT).** *Proc ASCO* 2004;**Abstract 4501**.

INTERVIEW

Ronald M Bukowski, MD

Dr Bukowski is Emeritus Staff and Consultant at the Cleveland Clinic Foundation's Taussig Cancer Center and is Professor of Medicine at the CCF Lerner College of Medicine of CWRU in Cleveland, Ohio.

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Track 5

DR LOVE: Can you discuss your presentation at ASCO 2008 evaluating sorafenib in older patients?

DR BUKOWSKI: It was an analysis of the Advanced Renal Cell Carcinoma Sorafenib (ARCCS) Expanded Access program. The question has been whether older patients experience the same benefits and toxicities as younger patients. The real issue is the definition of old, and no one agrees. The cutoff of 65 years old was chosen (Bukowski 2008). In this study with more than 2,500 patients enrolled by community doctors, we evaluated whether older patients and

younger patients had similar progression-free survival (PFS) rates and toxicities associated with sorafenib.

It turns out that they did. An increase in toxicities did not appear in the individuals older than age 65 (Bukowski 2008; [3.1]).

3.1

Advanced Renal Cell Carcinoma Sorafenib (ARCCS) Expanded Access Program: Subset Analysis in Elderly Patients

EFFICACY

	>65 years old (n = 775)	≤65 years old (n = 1,112)
Complete response	0	<1%
Partial response	3%	4%
Stable disease	81%	79%
Median progression-free survival	38.1 weeks	34.9 weeks
Median overall survival	46.6 weeks	50.3 weeks

SAFETY: Grade ≥III adverse events

	≥65 years old (n = 1,135)	<65 years old (n = 1,361)
Hand-foot skin reaction	9%	10%
Rash/desquamation	6%	4%
Fatigue	8%	4%
Hypertension	5%	5%
Diarrhea	3%	3%
Nausea	2%	3%
Anorexia	2%	2%

SOURCE: Bukowski RM et al. *Proc ASCO* 2008;**Abstract 5045**.

Track 6

DR LOVE: Would you review the AVOREN trial and the update presented at ASCO 2008?

DR BUKOWSKI: The AVOREN trial was a straightforward study in which bevacizumab/interferon was compared to interferon alone as first-line therapy for mRCC. Last year, the presentation focused on efficacy and demonstrated that PFS was basically doubled when combining bevacizumab with interferon. The response rate was likewise doubled from 15 to 30 percent (Escudier 2007).

In the presentation this year, Dr Escudier evaluated the patients who had interferon dose reductions. As one would expect, patients tolerated lower doses of interferon better than higher doses. Outcomes were also studied. Although it was a subset analysis, which needs to be conducted in that context, it showed no difference between patients who had interferon dose reductions and those who did not (Escudier 2008; Melichar 2008; [3.2]).

3.2

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

Parameter	Reduced-dose IFN		Full-dose IFN		Total population	
	Bev + IFN (n = 124[a])	IFN + placebo (n = 90[a])	Bev + IFN (n = 174[a])	IFN + placebo (n = 186[a])	Bev + IFN (n = 298[a])	IFN + placebo (n = 276[a])
Overall response	34%	17% $p = 0.0181$	31%	12% $p < 0.0001$	32%	13% $p < 0.0001$
Median duration of response[b]	13.6mo	8.3mo	13.5mo	14.0mo	13.5mo	11.1mo

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

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

Is a lower dose of interferon sufficient and clearly easier to tolerate than the one used in the study? These data support that. They even address the issue of whether interferon is completely necessary.

As you reduce the dose, perhaps you can almost eliminate the drug. We cannot, however, do so at this point. So lower doses of interferon are acceptable. I believe that most physicians who have used interferon recognize that you can administer two or three million units three times per week easily compared to nine or 18 million units, with which the toxicity is much higher.

Track 7

DR LOVE: You led a study evaluating bevacizumab alone versus bevacizumab with erlotinib. How much do you think interferon is contributing to the activity of bevacizumab?

DR BUKOWSKI: I wish we had an answer because it would make our lives easier as we begin to use bevacizumab for renal cancer in the United States. All we have are the data I presented and published, which included approximately 100 patients — half received bevacizumab alone, and the other half received bevacizumab and erlotinib (Bukowski 2007; [1.3, page 6]).

Erlotinib didn't have any effect except the usual toxicity. The median PFS for the group as a whole was approximately nine months. We saw little difference in the median PFS between the two arms — one was a little less than nine months and the other a little more than nine months. The response rates in both arms were in the range of 13 to 14 percent (Bukowski 2007; [1.3, page 6]). This would be our de facto bevacizumab monotherapy experience that is available in a randomized, blinded setting.

When we view the data from AVOREN (Escudier 2007) and CALGB-90206 (Rini 2008; [3.3]) — two large groups of patients treated with the combination of bevacizumab and interferon — both show an effect on progression.

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

	Bevacizumab + IFN	IFN
Median time to progression	8.5 months*	5.2 months
Overall response rate (ORR)	25.5%*	13.1%
Grade III hypertension	10%	0%
Anorexia	17%	8%
Fatigue	37%	30%
Proteinuria	15%	<1%

* $p < 0.0001$

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

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

In the AVOREN study, the median PFS was approximately 10.2 months. In CALGB-90206, the median time to progression was 8.5 months.

You come away thinking that monotherapy with bevacizumab, if indeed one can extrapolate from the erlotinib/bevacizumab trial, is almost equivalent with perhaps a 1.5-month lower median PFS than with the combination of interferon and bevacizumab. You have the sense that the major contribution is from bevacizumab. My impression is that if we had a well-designed study in which we used bevacizumab monotherapy, we would see a median PFS of nine to 10 months.

Track 16

DR LOVE: Which new research strategies are currently receiving high priority?

DR BUKOWSKI: The data that keep coming out are with combinations, which is the next frontier. Can we combine these drugs in a fashion that enhances efficacy? We don't know. I caution people against prematurely using combinations at this point because we have seen toxicity that is worrisome and problematic.

One paper, presented for the third time, was the Phase I trial of sorafenib and bevacizumab conducted by Jeff Sosman. The response rate remains robust at about 40 percent, but the toxicity is clearly problematic. One needs to reduce the doses of both bevacizumab and sorafenib to make the combination tolerable (Sosman 2008).

The other intriguing combination is sunitinib/bevacizumab, which has been studied at two centers — Memorial Sloan-Kettering (Feldman 2008) and the Cleveland Clinic (Cooney 2008). The outcomes at Memorial were such

that you could administer full doses of both drugs, but within a cycle or two, toxicity developed that was a problem.

We saw three or four cases of hemolytic uremic syndrome, which is difficult to manage and could be life threatening. The combination at full doses was abandoned in terms of further studies.

At the Cleveland Clinic, we've not seen a single case of hemolytic uremic syndrome, but many of our patients, as they continue therapy, have had dose reductions because of other toxicities. You come away thinking that the tyrosine kinase inhibitors sorafenib and sunitinib are sometimes difficult to combine with other agents.

However, bevacizumab appears to be a drug that you can combine with other agents, especially with the mTOR inhibitors. A lot of interest exists for the combinations of bevacizumab with temsirolimus or everolimus.

Right now, it's fair to say that the data on combinations are preliminary. We don't have evidence to say that they are tolerated long term or that efficacy will be improved. ■

SELECT PUBLICATIONS

Bukowski RM et al. **Safety and efficacy of sorafenib in elderly patients (pts) >65 years: A subset analysis from the Advanced Renal Cell Carcinoma Sorafenib (ARCCS) Expanded Access Program in North America.** *Proc ASCO* 2008;**Abstract 5045**.

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

Cooney MM et al. **Sunitinib and bevacizumab in advanced solid tumors: A phase I trial.** *Proc ASCO* 2008;**Abstract 3530**.

Escudier BJ et al. **Update on AVOREN trial in metastatic renal cell carcinoma (mRCC): Efficacy and safety in subgroups of patients (pts) and pharmacokinetic (PK) analysis.** *Proc ASCO* 2008;**Abstract 5025**.

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

Feldman DR et al. **Phase I trial of bevacizumab plus sunitinib in patients with metastatic renal cell carcinoma.** *Proc ASCO* 2008;**Abstract 5100**.

Hainsworth JD et al. **Treatment of metastatic renal cell carcinoma with a combination of bevacizumab and erlotinib.** *J Clin Oncol* 2005;23(31):7889-96. **Abstract**

Melichar B et al. **First-line bevacizumab combined with reduced dose interferon-{alpha}2a is active in patients with metastatic renal cell carcinoma.** *Ann Oncol* 2008;19(8):1470-6. **Abstract**

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

Sosman JA et al. **Updated results of phase I trial of sorafenib (S) and bevacizumab (B) in patients with metastatic renal cell cancer (mRCC).** *Proc ASCO* 2008;**Abstract 5011**.

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the Phase III trial for patients with previously untreated metastatic renal cell carcinoma, sunitinib resulted in significant improvement in _____ compared to interferon.**
   a. Objective response rate
   b. Progression-free survival
   c. Overall survival
   d. All of the above

2. **In the Phase III trial of sunitinib versus interferon for patients with previously untreated metastatic renal cell carcinoma, _____ percent of patients receiving sunitinib experienced clinical benefit.**
   a. 20
   b. 40
   c. 60
   d. 80

3. **RAD001 (everolimus) improves progression-free survival for patients whose disease previously progressed after treatment with _____.**
   a. Sorafenib
   b. Sunitinib
   c. Either a or b
   d. None of the above

4. **Which of the following is the most common side effect of mTOR inhibitors?**
   a. Stomatitis
   b. Fatigue
   c. Pulmonary toxicity
   d. Microangiopathic syndrome

5. **Temsirolimus is currently available only in an IV formulation, whereas everolimus is available only in an oral formulation.**
   a. True
   b. False

6. **The BeST trial (ECOG-E2804) will evaluate single-agent bevacizumab versus which of the following combination therapies?**
   a. Temsirolimus/bevacizumab
   b. Sorafenib/bevacizumab
   c. Temsirolimus/sorafenib
   d. All of the above

7. **The ASSURE trial will compare adjuvant sorafenib to _____ for patients with locally advanced renal cell carcinoma.**
   a. Temsirolimus
   b. Everolimus
   c. Bevacizumab
   d. Sunitinib

8. **In an analysis of the ARCCS Expanded Access trial, elderly patients and younger patients had similar _____.**
   a. Progression-free survivals
   b. Toxicities
   c. Both a and b
   d. None of the above

9. **In a subset analysis of the AVOREN trial, patients who received reduced doses of interferon in combination with bevacizumab had _____ efficacy outcomes compared to those who received full doses of interferon in combination with bevacizumab.**
   a. Better
   b. Worse
   c. Similar

10. **Among patients with previously untreated metastatic renal cell carcinoma, the addition of erlotinib to bevacizumab improved both the response rate and the progression-free survival rate.**
    a. True
    b. False

11. **Which of the following trials have evaluated bevacizumab in combination with interferon?**
    a. AVOREN
    b. CALGB-90206
    c. ARCCS
    d. Both a and b
    e. All of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Renal Cell Cancer Update — Issue 2, 2008

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

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

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

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Data regarding sunitinib versus interferon as first-line therapy for mRCC 4 3 2 1
- Efficacy and tolerability of sorafenib in older and younger patients 4 3 2 1
- Outcomes of the use of RAD001, everolimus, for mRCC after disease progression on sunitinib or sorafenib 4 3 2 1
- Impact of dose reduction of interferon or combination with bevacizumab in the AVOREN trial 4 3 2 1

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

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Data regarding sunitinib versus interferon as first-line therapy for mRCC 4 3 2 1
- Efficacy and tolerability of sorafenib in older and younger patients 4 3 2 1
- Outcomes of the use of RAD001, everolimus, for mRCC after disease progression on sunitinib or sorafenib 4 3 2 1
- Impact of dose reduction of interferon or combination with bevacizumab in the AVOREN trial 4 3 2 1

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

☐ Yes ☐ No

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

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

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

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

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

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

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

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

- Apply an understanding of the biology of clear cell RCC, including inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene and the pathway leading to VEGF overexpression, to therapeutic decision-making. . . . . 4 3 2 1 N/M N/A
- Develop management strategies for advanced RCC, considering the safety and efficacy profiles of targeted biologic therapies inhibiting VEGF, PDGF and EGF receptors. . . . . 4 3 2 1 N/M N/A
- Review clinical efficacy and safety data for inhibitors of the mammalian target of rapamycin (mTOR), and develop a plan for incorporating these agents into treatment plans for advanced RCC. . . . . 4 3 2 1 N/M N/A
- Evaluate emerging data on the safety and efficacy of combining targeted therapies for patients with RCC, and apply this information to clinical practice. . . . . 4 3 2 1 N/M N/A
- Devise treatment plans for patients with RCC, considering molecular targets and the pathologic grade of the tumor. . . . . 4 3 2 1 N/M N/A
- Develop an approach for the sequencing and duration of treatment with targeted biologic therapies. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with RCC about potential participation in ongoing clinical trials in the adjuvant and metastatic settings. . . . . 4 3 2 1 N/M N/A

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

. . . . . .

. . . . . .

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

.....

Additional comments about this activity:

.....

.....

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

☐ Yes ☐ No

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

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Robert A Figlin, MD	4 3 2 1	4 3 2 1
Gary R Hudes, MD	4 3 2 1	4 3 2 1
Ronald M Bukowski, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty for this activity:

.....

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Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: DrNeilLove@ResearchToPractice.com
For CME/CNE Information	Email: CE@ResearchToPractice.com

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U P D A T E

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