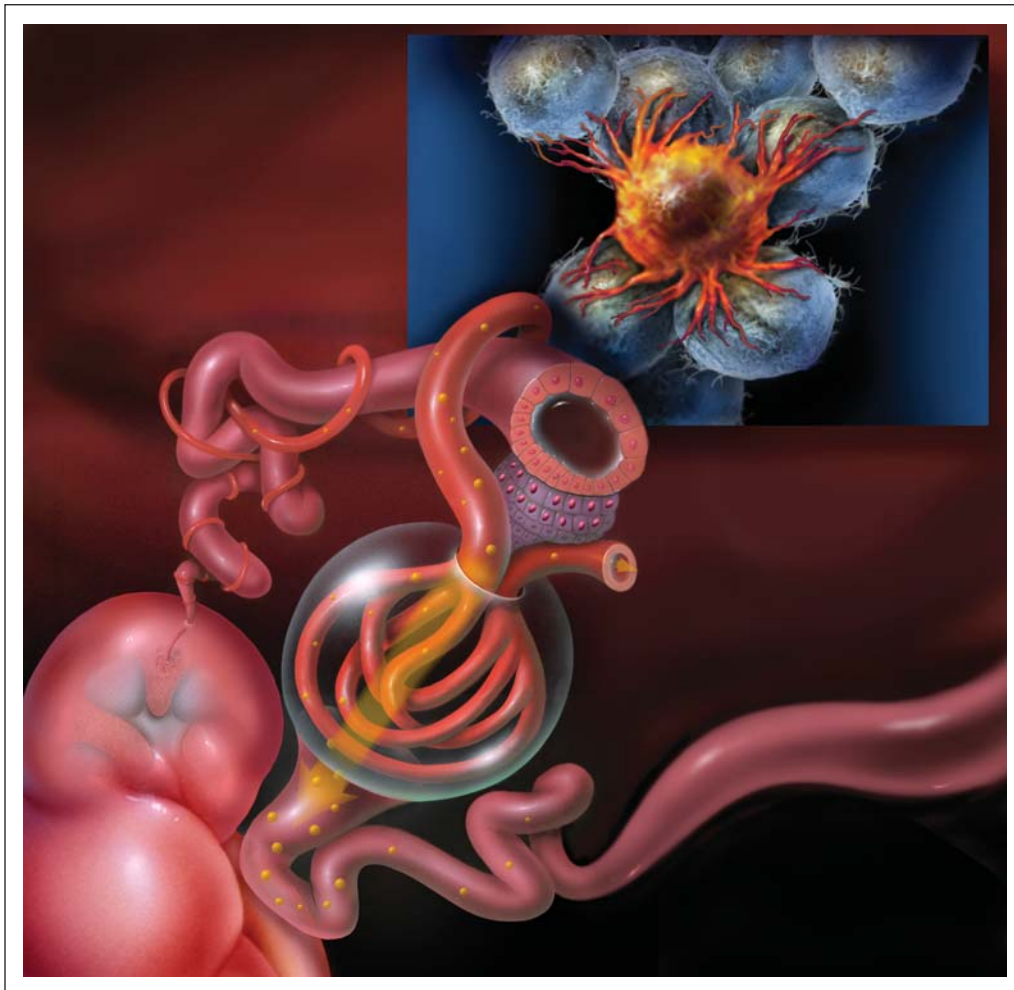


ADVANCES IN
**KIDNEY
CANCER**

An educational service for medical oncologists and urologists Winter 2006-2007



Special Report

**Clinical Highlights from
The Fifth International Kidney Cancer Symposium**

- New Concepts in Combining Novel and Targeted Therapies for Metastatic RCC
- Current Approaches in Nephron-Sparing and Minimally Invasive Surgeries
 - Advances in Imaging
 - Identifying New Biomarkers

A Supplement to the *Kidney Cancer Journal*

Editorial Mission

Advances in Kidney Cancer is provided as an educational service to medical oncologists and urologists and as a supplement to the *Kidney Cancer Journal*. Featuring selected highlights from the Fifth International Kidney Cancer Symposium, September 22-23, 2006, Chicago, *Advances in Kidney Cancer* will enable physicians to recognize important trends in the diagnosis and management of renal cell carcinoma affecting clinical practice. Analyzing new data presented at the Symposium, this report covers a broad spectrum of topics, including novel and targeted therapies, molecular markers, histology, minimally invasive surgery, and recent advances in imaging techniques. The Symposium was sponsored by the Kidney Cancer Association and the Cleveland Clinic Foundation. All content was peer reviewed by the Associate Editors and the Editor-in-Chief.

Editor-in-Chief

Robert A. Figlin, MD

Arthur and Rosalie Kaplan Chair in Oncology Professor and Chair, Medical Oncology and Therapeutics Research
City of Hope National Medical Center and Beckman Research Institute
Associate Director for Clinical Research
City of Hope Comprehensive Cancer Center
Duarte, California

Associate Editors

Ronald M. Bukowski, MD

Director, Department of Experimental Therapeutics
Cleveland Clinic Taussig Cancer Center
Cleveland, Ohio

Robert J. Motzer, MD

Attending Physician, Memorial Sloan-Kettering Cancer Center
New York City
Professor of Medicine
Weill Medical College of Cornell University
Ithaca, New York

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Michael McClain, Design Director

Editorial Offices

Genitourinary Publishing
P.O. Box 1688, Westhampton Beach, NY 11978
Tel: (631) 288-7733 Fax (631) 288-7744

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About the Cover

Artist's conception of a normal kidney and related anatomical structures with renal cell carcinoma cell superimposed in the upper right. (Copyright Alexander & Turner Medical Illustration Studio, 2006).

Editor's Memo

2006: A Hard Act to Follow in Kidney Cancer, But Expectations for 2007 and Beyond Remain High



Robert A. Figlin, MD



Ronald M. Bukowski, MD



Robert J. Motzer, MD

Although extraordinary progress in kidney cancer makes 2006 a hard act to follow, we are all looking forward to the next meeting of the American Society of Clinical Oncology (ASCO) when new information on the use of recently approved targeted agents is expected. ASCO is the benchmark for such progress, but numerous meetings during the year not only keep us informed about ongoing developments but provide comprehensive follow-up to the ASCO data. The Fifth International Kidney Cancer Symposium, which attracted a record crowd of more than 320 attendees in Chicago, September 22-23, offers a great vehicle for the most in-depth review and analysis of new data in renal cell carcinoma (RCC) available to practicing clinicians and investigators.

Advances in Kidney Cancer reflects selected highlights from this meeting sponsored every year by the Kidney Cancer Association. Two esteemed colleagues and principal investigators, Ronald Bukowski, MD, and Robert Motzer, MD, who serve as Associate Editors of this publication, provided insights and perspectives on the proceedings as we seek to recap some of the essential information from this meeting, with special emphasis on advances in therapy. Although the approval of the new targeted therapies was the major story to emerge during the last year, the next generation of clinical trials is under way, focused on exploring combinations of these compounds and whether the sequence of their administration will enhance their efficacy through the vertical or horizontal inhibition of different pathways.

Currently, phase 3 trials have shown a benefit of sunitinib, considered the new reference standard, and temsirolimus, specifically in poor risk patients, over IFN-alpha in first line therapy, and sorafenib over placebo as a second line therapy. There are pivotal phase 3 trials that are under way or being conducted for bevacizumab, pazopanib, and RAD001, a new mTOR inhibitor.

With regard to the types of combinations, the categories include new VHL-targeted therapies with cytotoxic agents, cytokines, other VHL-targeted agents, or agents that interrupt or influence other pathways.

The Symposium addressed many other topics of major interest, including the role of nephron-sparing surgery and other minimally invasive approaches to manage RCC, and recent advances in identifying molecular markers and targets for therapy. One of the advantages and appeals of a smaller meeting such as this symposium is that it gathers all of the presenters and experts in one location; this venue eliminates the need to hurry to far-flung sessions scattered throughout a giant convention center and gives attendees convenient access to presenters, posters, and all discussions.

If you were unable to attend the meeting, virtually all of the presentations are also gathered in one online location as a streaming video—the Kidney Cancer Association website. I urge you to visit the website at <http://www.curekidneycancer.org>, click on the Physician Education (CME) link and view the videos at your convenience. All of the slides presented at the Symposium are also featured in the video. Make sure your browser is the latest version (IE 6.0 is acceptable and IE 7.0 is best) and that Java is updated: www.java.com (verify and download).

Robert A. Figlin, MD
Editor-in-Chief

Supported by an unrestricted educational grant from Pfizer Oncology

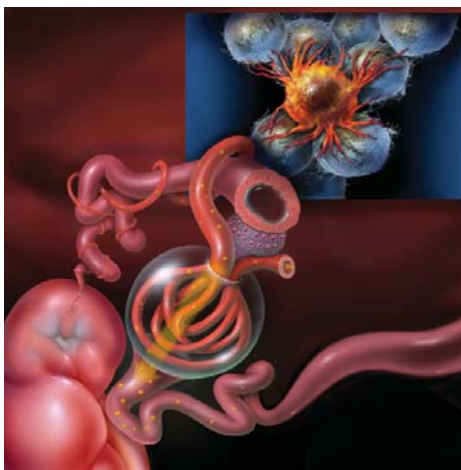
Advances in Renal Cell Carcinoma: Selected Highlights from the Fifth International Kidney Cancer Symposium

“With the identification of multiple targeted drugs that show activity for renal cell carcinoma, the groundwork has been established for an entire framework of studies poised to address additional questions that we need to resolve over the next few years,” said Robert Motzer, Attending Physician, Memorial Sloan-Kettering Cancer Center, New York. This year’s Fifth International Kidney Cancer Symposium picked up on themes and directions from the 2006 meeting of the American Society of Clinical Oncology (ASCO), reviewing progress made but suggesting the shape of things to come, including the hypotheses generated by new clinical trials under way or planned.

One of the hypotheses undergoing study is whether combinations of these new agents are likely to be more effective than any of the targeted formulations used as monotherapy. “We need to study whether there is a role for combination therapy and what the best sequence of these agents will be,” added Dr Motzer.

The paradigm established by ASCO remains the benchmark, but the new trials moving forward are expected to produce new strategies and novel approaches as investigators explore their use through the next generation of phase 3 trials. Some results from these new trials are expected at the 2007 meeting of ASCO. Based on the approach presented at ASCO and reviewed at the International Symposium of the Kidney Cancer Association, the treatment algorithm incorporates the following points:

- In good and intermediate risk patients or a relatively general population of patients, sunitinib is considered the “reference standard.”
- For a selected group of patients, however, high-dose interleukin-2 (IL-2) remains an option, although it is incumbent on investigators to better select which patients should receive high-dose IL-2 for this treatment to maintain a foothold on the therapeutic frontline.
- For poor-risk patients, temsirolimus (not yet approved by



the FDA) is a reasonable option as first-line therapy and for cytokine failures, sorafenib is an appropriate choice. For VEGF receptor or mTOR inhibitor failures, a group expected to grow during the next few years, the appropriate therapy remains to be established.

Novel Therapy for RCC: Update on Randomized Phase 2/3 Trials

Sunitinib (Sutent) vs IFN-alpha. The paradigm-changing study, covered by Dr Motzer, is a phase 3 randomized trial that elevated sunitinib to first-line,

based on data from a multicenter, international trial.

The data from Dr Motzer on sunitinib included the following:

- Mean progression-free survival (the primary endpoint) was 11 months for sunitinib vs 5 months for interferon-alpha ($P < .000001$) in patients with good to intermediate risk, based on results in 750 patients (**Figure 1**).
- Sunitinib produced an overall response rate of 31% vs 6% associated with interferon (IFN)-alpha. ($P < .000001$).
- The benefit with sunitinib was apparent across all prognostic subgroups studied.
- Sunitinib had an acceptable safety profile.

To be eligible for the trial, the following criteria needed to be met: metastatic RCC with clear cell histology; measurable disease by RECIST criteria; no prior systemic therapy; good performance status; and adequate blood counts and serum chemistry. Patients received 50 mg of sunitinib daily for 4 weeks followed by 2 weeks off for a median of 6 months. The objective response rate was 31% for the sunitinib groups vs 6% for the IFN-alpha group.

Sorafenib (Nexavar) vs placebo. An update of results from TARGETs (Treatment Approaches in Renal Cancer Global Evaluation Trial) reconfirmed the role of sorafenib in the paradigm of targeted therapy. Thomas Hutson, DO, PharmD,

Director of the GU Oncology Program at the Baylor Sammon Cancer Center, Houston, Texas, reported on progression-free survival and the impact of crossover on overall survival among patients who moved on to the sorafenib arm of the study from placebo. Highlights included:

- 50% of placebo patients crossed over to sorafenib.
- A persistent overall survival benefit with sorafenib was noted even after crossover: overall survival improved by 30%.
- Sorafenib significantly prolonged progression-free survival (5.5 months) compared with placebo (2.8 months) in advanced RCC.
- Median survival for patients receiving placebo was 14.7 months; a median survival for patients on sorafenib has not yet been reached.
- 84% of patients had stable disease or better according to RECIST criteria.

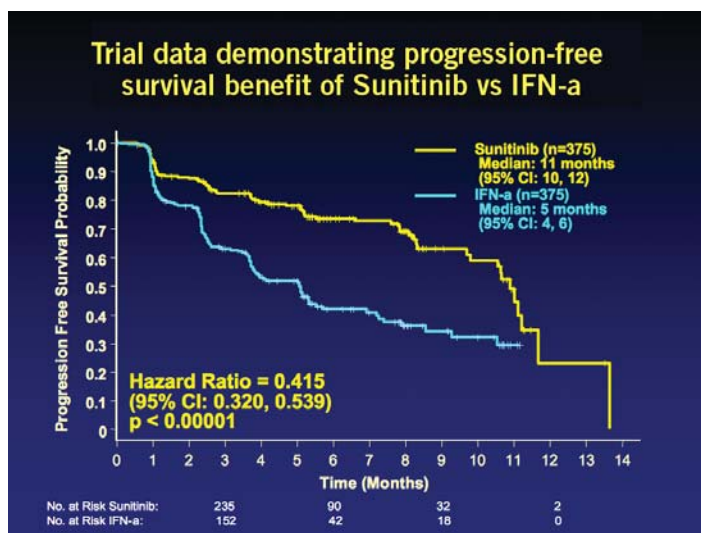


Figure 1.

The global ARCC trial: Temsirolimus or IFN or combination of temsirolimus + IFN in poor-risk patients. Growing interest in temsirolimus, a specific inhibitor of the mTOR pathway, is likely to build in the first quarter of 2007 as this agent undergoes further study in a poor-risk population. At ASCO 2006, it was recommended as part of the paradigm as possible first-line treatment in this subgroup of patients. Although not yet approved by the FDA, results point toward application of this mTOR inhibitor as part of possible combination therapy.

The phase 3 study from Hudes et al featured 3 arms, temsirolimus vs IFN-alpha and the combination of temsirolimus and IFN-alpha, and involved 626 patients in 26 countries and 209 sites. The key findings suggested:

- Temsirolimus, as a single agent, significantly improved overall survival and progression-free survival of patients with metastatic RCC and poor-risk features as compared with IFN. There was a:
 - 3.6 month (49%) improvement in median overall survival.
 - 1.8 month (95%) improvement in median PFS.

- The overall survival and PFS benefits of temsirolimus 25 mg IV weekly as compared with IFN were not further improved with the combination of temsirolimus 15 mg IV weekly and interferon 6 MU tiw.
- Temsirolimus was better tolerated than IFN with a 16% reduction in the proportion of patients with grade ≥ 3 adverse events.
- Temsirolimus 25 mg IV weekly can be considered standard first-line therapy for patients with metastatic RCC and poor-risk features.
- The results of this global phase 3 trial demonstrate that mTOR is an important therapeutic target in RCC.

Clinical trials with bevacizumab in metastatic RCC.

With publication of the landmark study by Yang et al in 2003, bevacizumab was recognized as a monoclonal antibody and inhibitor of vascular endothelial growth factor (VEGF). Although not yet approved for renal cancer, bevacizumab remains a focus of numerous studies, either as monotherapy or in combination with other agents, particularly because it is generally regarded as the easiest of the targeted therapies to administer based on its favorable side effect profile, according to Ronald M. Bukowski, Director, Experimental Therapeutic Program, Cleveland Clinic Foundation Taussig Cancer Center, Cleveland, Ohio. Updating findings from a phase 2 study combining bevacizumab with erlotinib, an epidermal growth factor inhibitor, Dr Bukowski reported that this combination did not produce a significant benefit.

However, results are pending from two large phase 3 trials in which bevacizumab is being used as first-line therapy, including the CALGB 90206 study and the Roche B017705 trials to compare its use as monotherapy or in combination with IFN-alpha. Combination trials with sunitinib, sorafenib, mTOR inhibitors, IL-2, and others are also in progress with some results expected during ASCO 2007. The role of bevacizumab as monotherapy in RCC is one of the most important issues and still needs to be delineated by further study in phase 3 protocols.

“We are early in the development of combination therapy and it is not clear whether monotherapy or sequential therapy is the optimal way to use these drugs. It will take another year or two to understand it and right now we are at the hypothesis-generating stage,” added Dr Bukowski.

Treatment of targeted therapy-refractory RCC. As targeted therapy has entered mainstream practice in metastatic RCC, one of the key questions to emerge is how disease refractory to such therapy should be managed. Brian Rini, MD, from the Department of Solid Tumor Oncology, Cleveland Clinic Taussig Cancer Center, addressed this issue, noting that eventual resistance to targeted therapy is likely in the vast majority of patients in whom such treatment is initially effective. Thus, the safety and clinical activity of agents in targeted therapy-refractory RCC patients is of interest.

Some indications as to what agents need to be studied in this setting were suggested by Dr Rini, who reported on the efficacy of sunitinib or sorafenib in bevacizumab-refractory

metastatic RCC. At this point additional data are needed to determine whether the sequential use of either of these agents, including their use after antiangiogenic therapy, will be of significant benefit. For example, when response rates of patients treated with prior sunitinib or sorafenib were evaluated:

- There was no association between type of prior therapy received and response to subsequent sunitinib or sorafenib.
- Treatment with sorafenib and sunitinib after antiangiogenic therapy is feasible, although the incidence and severity of toxicity require prospective studies.

As the experience with targeted therapy grows, questions remain about how to define refractory in various subsets of patients undergoing targeted therapy. For example, Dr Rini noted that there are different patterns of failure and mechanism of resistance and thus, treatment decisions may be different. Also, is cytokine therapy, especially high-dose interleukin-2 (IL-2) feasible after targeted therapy?

Prognostic factors in metastatic RCC. Historically, a number of well-designed, retrospective analyses of prognostic factors for survival in metastatic RCC have been reported in the literature. Efforts to refine these factors are currently under way through a broadly based investigative group. The International Kidney Cancer Working Group was organized in 2002 to develop and contribute to a database of clinical prognostic factors for survival in metastatic RCC, according to Paul J. Elson, ScD, a member of the Associate Staff of the Cleveland Clinic Department of Quantitative Health Sciences and the Taussig Cancer Center. Dr Elson delineated how this research is progressing as he presented preliminary data compiled on 3,780 patients from 11 scientific groups such as the Cleveland Clinic, UCLA, and the University of Washington. Preliminary data from the accrual period of 1975-2002 showed that 75% of these patients had prior nephrectomy, 88% had died, with a median survival of 11.3

months. In a univariate analysis, only age and gender from the following list did not show an impact on survival:

Demographic and Clinical—race; ECOG performance status; recent weight loss; diagnosis date; TNM stage at diagnosis; date of diagnosis for metastatic disease; prior nephrectomy; prior radiotherapy; involved kidney; sites of metastatic disease; entry date on study; and treatment. *Biochemical*—hemoglobin; WBC; neutrophils; lymphocytes; monocytes; sedimentation rate; CRP; creatinine; alkaline phosphatase; LDH; albumin; and calcium. *Pathological*—grade and histology.

Expanded access program of sunitinib for refractory metastatic RCC. An estimated 3,000 patients worldwide are expected to participate in an expanded access program for patients with metastatic RCC who were not eligible to participate in ongoing studies of this drug, according to Janice P. Dutcher, MD, Associate Director, Our Lady of Mercy Comprehensive Cancer Center, Bronx, New York. Among the inclusion criteria are the following: refractory to at least two prior systemic anticancer treatments; adequate organ function; and resolution of all acute toxic effects or prior therapy to at least less than grade 1 as defined by the National Cancer Institute criteria.

Although a small number of patients have been analyzed to date (43 at Cleveland Clinic and 6 at Our Lady of Mercy), results from the trial may provide better insights into dosing and identification of other patient populations who may benefit from sunitinib administration. From a phase 2 study, Dr Dutcher presented some results regarding sunitinib that lead to a number of questions:

- Once we have maximal response, and PET negativity, do we need to combine TKIs?
- What criteria should be used to discontinue the drug?
- Will we see re-responses with TKIs as we have with bevacizumab?
- What is the etiology of the cardiotoxicity (hypertension, most commonly)?

SUTENT® (sunitinib malate)

is approved for patients with advanced renal cell carcinoma (RCC). Approval for advanced RCC is based on partial response rates and duration of responses. There are no randomized trials of SUTENT demonstrating clinical benefit such as increased survival or improvement in disease-related symptoms in RCC.

UNLOCK THE POSSIBILITIES IN



SUTENT is contraindicated in patients with hypersensitivity to any component of SUTENT.

Pregnancy Category D—Animal data suggest potential for human fetal harm. Women should be advised against breast-feeding while taking SUTENT.

Decreases in left ventricular ejection fraction (LVEF) to below lower limit of normal have been observed. Three patients (1%) on SUTENT had grade 3 reductions in LVEF to <40%; 2 patients died without receiving further study drug. Patients who presented with cardiac, pulmonary embolism, or cerebrovascular events within 12 months prior to SUTENT administration were excluded from SUTENT clinical studies. It is unknown whether patients with concomitant cardiac conditions are at higher risk for developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. These patients should be carefully monitored for clinical signs and symptoms of CHF. Baseline and periodic evaluations of LVEF should be considered. In the presence of clinical manifestations of CHF, discontinuation is recommended. The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with LVEF <50% and >20% below baseline.

Bleeding events occurred in 26% of patients receiving SUTENT for RCC. Epistaxis was the most common hemorrhagic AE reported.

Patients should be monitored for hypertension and treated as needed with antihypertensive therapy. In severe hypertension, temporary suspension of SUTENT is recommended.

CBCs with platelet count and serum chemistries should be performed at the beginning of each treatment cycle.

Physicians are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma, or severe infection.

In clinical studies of SUTENT, seizures have been observed in subjects with radiological evidence of brain metastases.

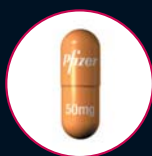
Dose interruptions occurred in 48 patients (45%) in Study 1 and 45 patients (71%) in Study 2.

Hypothyroidism was reported in 4% of patients in RCC trials. Patients with symptoms of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Dose adjustments are recommended when administered with CYP3A4 inhibitors or inducers.

Reference: 1. Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2006;24:16-24.

Please see brief summary of prescribing information on last page.

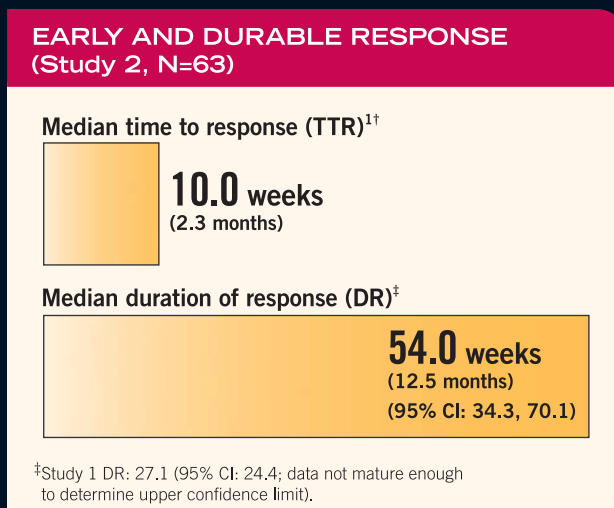
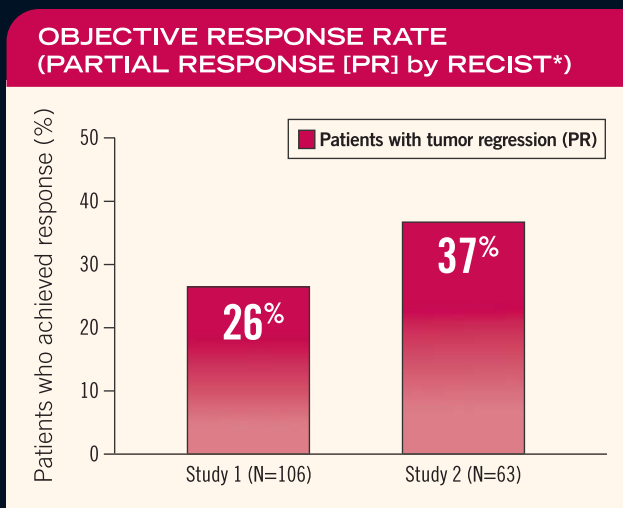


SUTENT UNLOCKS THE POSSIBILITIES IN RCC

➤ **An oral multi-kinase inhibitor**—SUTENT inhibits multiple signaling pathways, resulting in a dual-action antiproliferative and antiangiogenic effect

Significant clinical efficacy

➤ **Proven in 2 phase II, single-arm, open-label, multicenter trials** of patients with cytokine-refractory RCC



Two separate phase II, single-arm, open-label, multicenter studies of patients with cytokine-refractory metastatic RCC. All patients received SUTENT 50 mg once daily in cycles of 4 weeks on/2 weeks off. Primary endpoint was objective response rate (partial + complete) by RECIST.

- **Response rate (PR) of 26% in Study 1 (95% CI: 17.5, 34.9)**
- **Response rate (PR) of 37% in Study 2 (95% CI: 24.7, 49.6)**
- **Median duration of response was one year (54.0 weeks) in Study 2**
- **Adverse events (AEs) were generally moderate**

- Treatment-emergent AEs included fatigue (74%), diarrhea (55%), nausea (54%), mucositis/stomatitis (53%), dyspepsia (46%), altered taste (43%), rash (38%), vomiting (37%), constipation (34%), skin discoloration (33%), anorexia (31%), hypertension (28%), dyspnea (28%), arthralgia (28%), bleeding, all sites (26%), headache (25%), abdominal pain (20%), peripheral edema (17%), glossodynia (15%), hand-foot syndrome (12%), peripheral neuropathy (10%), appetite disturbance (9%), blistering of the skin (7%), and periorbital edema (7%)
- Grade 3 or 4 AEs included lymphopenia (21%), increased lipase (16%), neutropenia (13%), fatigue (11%), hypophosphatemia (10%), hyperuricemia (10%), leukopenia (7%), anemia (7%), hypertension (6%), diarrhea (5%), dyspnea (5%), increased amylase (5%), mucositis/stomatitis (4%), vomiting (4%), hand-foot syndrome (3%), dehydration (3%), abdominal pain (3%), and thrombocytopenia (3%)

*RECIST=Response Evaluation Criteria in Solid Tumors.
†Retrospective analysis.

For more information, please visit www.sutent.com and www.pfizeroncology.com



SUTENT® (SUNITINIB MALATE) CAPSULES

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: SUTENT is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.

SUTENT is indicated for the treatment of advanced renal cell carcinoma. Approval for advanced renal cell carcinoma is based on partial response rates and duration of responses. There are no randomized trials of SUTENT demonstrating clinical benefit such as increased survival or improvement in disease-related symptoms in renal cell carcinoma.

CONTRAINDICATIONS: Use of SUTENT is contraindicated in patients with hypersensitivity to sunitinib malate or to any other component of SUTENT.

WARNINGS: Pregnancy Category D. Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1.5, 5.0 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure in patients administered the recommended daily doses (RDD)). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥ 1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤ 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD). As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT should be expected to result in adverse effects on pregnancy. There are no adequate and well-controlled studies of SUTENT in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

PRECAUTIONS: Adverse events described in the following sections for MRCC patients are derived from Study 1 and Study 2. Adverse events discussed for GIST patients are derived from Study A, the randomized, placebo-controlled trial. (See CLINICAL STUDIES in full prescribing information). **Left Ventricular Dysfunction.** In the two MRCC studies, twenty-five patients (15%) had decreases in left ventricular ejection fraction (LVEF) to below the lower limit of normal (LLN). In GIST Study A, 22 patients (11%) on SUTENT and 3 patients (3%) on placebo had treatment-emergent LVEF values below the LLN. Nine of twenty-two GIST patients on SUTENT with LVEF changes recovered without intervention. Five patients had documented LVEF recovery following intervention (dose reduction - 1 patient; addition of antihypertensive or diuretic medications - 4 patients). Six patients went off study without documented recovery. Additionally, three patients (1%) on SUTENT had Grade 3 reductions in left ventricular systolic function to LVEF $< 40\%$; two of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF. In GIST Study A, 1 patient ($< 1\%$) on SUTENT and 1 patient (1%) on placebo died of diagnosed heart failure; 2 patients (1%) on SUTENT and 2 patients (2%) on placebo died of treatment-emergent cardiac arrest. Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. **These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered. In the presence of clinical manifestations of CHF, discontinuation of SUTENT is recommended.** The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction $< 50\%$ and $> 20\%$ below baseline. **Hemorrhagic Events.** Bleeding events occurred in 44/169 patients (26%) receiving SUTENT for MRCC and 37/202 patients (18%) receiving SUTENT in GIST Study A, compared to 17/102 patients (17%) receiving placebo. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events in MRCC or GIST patients included rectal, gingival, and GU, genital, and wound bleeding. Most events in MRCC patients were Grade 1 or 2; there was one Grade 3 event (bleeding foot wound). In GIST Study A, 14/202 patients (7%) receiving SUTENT and 9/102 patients (9%) on placebo had Grade 3 or 4 bleeding events. In addition, one patient in Study A taking placebo had a fatal gastrointestinal bleeding event during cycle 2. Tumor-related hemorrhage has been observed in patients treated with SUTENT. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life threatening hemoptysis or pulmonary hemorrhage. Fatal pulmonary hemorrhage occurred in 2 patients receiving SUTENT on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. SUTENT is not approved for use in patients with NSCLC. Treatment-emergent Grade 3 and 4 tumor hemorrhage occurred in 5 of 202 patients (3%) with GIST receiving SUTENT on Study A. Tumor hemorrhages were observed as early as cycle 1 and as late as cycle 6. One of these five patients received no further drug following tumor hemorrhage. None of the other four patients discontinued treatment or experienced dose delay due to tumor hemorrhage. No patients with GIST in the Study A placebo arm were observed to undergo intratumoral hemorrhage. Tumor hemorrhage has not been observed in patients with MRCC. Clinical assessments of these events should include serial complete blood counts (CBCs) and physical examinations. Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT. **Hypertension.** Hypertension (all grades) was reported in 48/169 MRCC patients (28%), 31/202 GIST patients on SUTENT (15%), and 11/102 GIST patients on placebo (11%). Grade 3 hypertension was reported in 10 MRCC patients (6%), 9 GIST patients on SUTENT (4%), and none of the GIST patients on placebo. No Grade 4 hypertension was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 6/169 MRCC patients (4%) and none of the patients in GIST Study A. No patients were discontinued from treatment with SUTENT due to systemic hypertension. Severe hypertension (> 200 mmHg systolic or 110 mmHg diastolic) occurred in 10/169 MRCC patients (6%), 8/202 GIST patients on SUTENT (4%), and 1/102 GIST patients on placebo (1%). Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled. **Adrenal Function.** Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of SUTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUTENT. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with SUTENT. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 mcg/dL (normal > 18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency. Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection. **Information for Patients.** Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received SUTENT. Supportive care for gastrointestinal adverse events requiring treatment may include anti-emetic or anti-diarrheal medication. Skin discoloration possibly due to the drug color (yellow) occurred in approximately 1/3 of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet. Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance. Patients should be advised to inform their health care providers of all concomitant medications, including over-the-counter medications and dietary supplements (see Drug Interactions). **Laboratory Tests.** CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT. **Drug Interactions.** Co-administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, azaravir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of SUTENT. Co-administration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease SUTENT plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly. SUTENT dose modification is recommended in patients using concomitant CYP3A4 inhibitors or inducers. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** Carcinogenicity studies with sunitinib have not been performed. Sunitinib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and in *in vivo* rat bone marrow micronucleus test. Effects on the female reproductive system were identified in a 3-month repeat dose monkey study (2, 6, 12 mg/kg/day), where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (approximately 5.1 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥ 2 mg/kg/day (approximately 0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 6 mg/kg/day in the 9-month monkey study (0.3, 1.5 and 6 mg/kg/day administered daily for 28 days followed by a 14 day respite; the 6 mg/kg dose produced a mean AUC that was approximately 0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month

study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months. Although fertility was not affected in rats, SUTENT may impair fertility in humans. In female rats, no fertility effects were observed at doses of ≤ 5.0 mg/kg/day (0.5, 1.5, 5.0 mg/kg/day) administered for 21 days up to gestational day 7; the 5.0 mg/kg dose produced an AUC that was approximately 5 times the AUC in patients administered the RDD, however significant embryolethality was observed at the 5.0 mg/kg dose. No reproductive effects were observed in male rats dosed (1, 3 or 10 mg/kg/day) for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤ 10 mg/kg/day (the 10-mg/kg/day dose produced a mean AUC that was approximately 25.8 times the AUC in patients administered the RDD). **Pregnancy Category D:** see WARNINGS. **Nursing Mothers.** Sunitinib and/or its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether SUTENT or its primary active metabolite are excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breastfeeding while taking SUTENT. **Pediatric Use.** The safety and efficacy of SUTENT in pediatric patients have not been studied in clinical trials. Physical dysplasia was observed in Cynomolgus monkeys with open growth plates treated for ≥ 3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were > 0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, 5.0 and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥ 5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at > 5 mg/kg. The incidence and severity of physical dysplasia were dose-related and were reversible upon cessation of treatment however findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was < 2 mg/kg/day. **Geriatric Use.** Of the 450 patients with solid tumors reported from clinical studies of SUTENT, 115 (25.6%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

ADVERSE REACTIONS: Overview. Four hundred fifty (450) patients with solid tumors including 257 patients (57% with GIST and 169 patients (38%) with cytotoxic-refractory MRCC have been treated in 7 completed non-randomized, open-label, single arm clinical trials and 1 randomized, double-blind, placebo-controlled clinical trial. All patients received SUTENT once daily as a 50-mg oral capsule on Schedule 42 (see CLINICAL STUDIES in full prescribing information). Adverse events occurring in MRCC studies are described below. **Adverse Events in the MRCC Studies.** The data described below reflect exposure to SUTENT in 169 patients with MRCC enrolled in Studies 1 and 2. The median duration of treatment was 5.5 months (range: 0.8-11.2) for Study 1 and 7.7 months (range: 0.2-16.1) for Study 2. Dose interruptions occurred in 48 patients (45%) on Study 1 and 45 patients (71%) on Study 2; one or more dose reductions occurred in 23 patients (22%) on Study 1 and 22 patients (35%) on Study 2. **The following information is taken from Table 6. Treatment-Emergent Adverse Events Reported in at Least 10% of MRCC Patients Treated with SUTENT® (MRCC [N=169]; Adverse Event, n (%); All Grades; Grade 3*, respectively -Any; 169 (100); 123 (73) -Constitutional / Fatigue; 125 (74); 19 (11); Fever; 26 (15); 2 (1) -Gastrointestinal / Diarrhea; 93 (55); 8 (5); Nausea; 92 (54); 4 (2); Mucositis/stomatitis; 90 (53); 7 (4); Dyspepsia; 77 (46); 1 (1); Vomiting; 63 (37); 7 (4); Constipation; 57 (34); 1 (1); Abdominal pain; 34 (20); 5 (3); Glossodynia; 25 (15); 0 (0); Flatulence; 24 (14); 0 (0) -Cardiac / Hypertension; 48 (28); 10 (6); Edema, peripheral; 28 (17); 1 (1) -Dermatology / Rash; 64 (38); 1 (1); Skin discoloration; 55 (33); 0 (0); Dry skin; 29 (17); 0 (0); Hair color changes; 29 (17); 0 (0); Hand-foot syndrome; 21 (12); 5 (3); Alopecia; 20 (12); 0 (0) -Neurology / Altered taste; 73 (43); 0 (0); Headache; 43 (25); 2 (1); Dizziness; 27 (16); 3 (2) -Musculoskeletal / Arthralgia; 48 (28); 2 (1); Pain in limb; 31 (18); 1 (1); Back pain; 29 (17); 1 (1); Myalgia; 29 (17); 1 (1) -Respiratory / Dyspnea; 47 (28); 8 (5); Cough; 29 (17); 1 (1) -Metabolism/Nutrition / Anorexia; 53 (31); 1 (1); Dehydration; 19 (11); 5 (3) -Hemorrhage/bleeding / Bleeding, all sites; 44 (26); 1 (1)**

*Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

**There were no Grade 4 adverse events among the events reported with $\geq 10\%$ incidence in the MRCC population.

Other significant adverse events occurring in MRCC patients receiving SUTENT included peripheral neuropathy (10%), appetite disturbance (9%), blistering of the skin (7%), periorbital edema (7%) and increased lacrimation (6%).

Treatment-Emergent Grade 3 and 4 Hematology Laboratory Abnormalities* from Studies 1 and 2

Laboratory Test	Unit	MRCC (N=169)		
		Grade 3	Grade 4	Total (Grade 3 + 4)
Hematology, n (%)		54 (32)	4 (2)	58 (34)
Neutropenia	10 ⁹ /L	21 (12)	1 (1)	22 (13)
Anemia	g/L	9 (5)	3 (2)	12 (7)
Lymphopenia	10 ⁹ /L	33 (20)	2 (1)	35 (21)
Thrombocytopenia	10 ⁹ /L	5 (3)	0 (0)	5 (3)
Leukopenia	10 ⁹ /L	12 (7)	0 (0)	12 (7)

*Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

Common treatment-emergent Grade 3 and 4 chemistry laboratory abnormalities in the MRCC studies included increased lipase (16%), increased amylase (5%), hypophosphatemia (10%), and hyperuricemia (10%). **Cardiovascular:** See PRECAUTIONS section for information on left ventricular dysfunction. Two patients with MRCC experienced Grade 3 myocardial ischemia, one had Grade 2 "cardiovascular toxicity" reported as an adverse event and one patient experienced a fatal myocardial infarction while on treatment. Data from non-clinical (*in vitro* and *in vivo*) studies indicate that sunitinib has the potential to inhibit the cardiac action potential repolarization process (e.g., prolongation of QT interval). In GIST Study A, 23 patients (11%) on SUTENT versus 12 (12%) on placebo had observed QT prolongation greater than 20 milliseconds from baseline. No consistent, clinically significant QTc prolongation has been observed in completed clinical studies. **Venous Thromboembolic Events:** Four patients (2%) on the two MRCC studies had venous thromboembolic events reported; two patients with pulmonary embolism (both Grade 4) and two patients with deep venous thrombosis (DVT) (both Grade 3). Dose interruption occurred in one of these cases. Seven patients (3%) on SUTENT and none on placebo in GIST Study A experienced venous thromboembolic events; five of the seven were Grade 3 DVTs, and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT. **Seizures:** In clinical studies of SUTENT, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, there have been rare ($< 1\%$) reports of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician. **Laboratory Abnormalities/Testing. Hematologic Events:** Grade 3 and 4 neutropenia were reported in 21 (13%) and 1 (1%) patients with MRCC, 19 (9%) and 3 (2%) patients with GIST on SUTENT, respectively. In Study A, one patient each in the SUTENT and placebo groups had febrile neutropenia. Grade 3 and 4 thrombocytopenia was reported in 5 (3%) and 0 patients with MRCC, 7 (4%) and 1 (1%) patients with GIST on SUTENT, respectively. No GIST patients receiving placebo experienced either Grade 3 or 4 neutropenia or thrombocytopenia. The rates of dose reductions and delays for hematologic abnormalities were 4% and 2% for neutropenia, 2% and 0% for anemia, and 1% and 1% for thrombocytopenia for MRCC and GIST patients, respectively. One MRCC patient with an adverse event report of Grade 4 thrombocytopenia discontinued treatment. Patients receiving SUTENT should be monitored regularly for myelosuppression. **Hypothyroidism:** Hypothyroidism was reported as an adverse event in 7 patients (4%) across the two MRCC studies. Additionally, TSH elevations were reported in 4 patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Treatment-emergent acquired hypothyroidism was noted in 8 GIST patients (4%) on SUTENT versus 1 (1%) on placebo. Patients with symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice. **Pancreatic Function:** Grade 3 and 4 increases in serum lipase were observed in 23 (14%) and 4 (2%), respectively, of 169 patients receiving SUTENT for MRCC. Grade 3 and 4 increases in serum amylase were observed in 8 (5%) and 1 (1%) MRCC patients, respectively. Increases in lipase levels were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with either MRCC or GIST. Pancreatitis has been observed rarely ($< 1\%$) in patients receiving SUTENT for GIST or MRCC. If symptoms of pancreatitis are present, patients should have SUTENT discontinued and be provided with appropriate supportive care.

OVERDOSAGE: No overdose of SUTENT was reported in completed clinical studies. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m²) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations. Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdose with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage.

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One of the key questions emerging after the approval of the new targeted therapies is whether combinations of agents can improve long-term outcomes while maintaining acceptable side effect profiles. Several trials—not yet mature—but providing hypotheses and rationales for various concurrent regimens are an important focus. These include: phase 1 and 2 studies of sorafenib and IFN- α ; phase 1 and 2 of sorafenib and bevacizumab; and the combination of sunitinib and bevacizumab.

Sorafenib and IFN- α . The rationale underlying this combination is that the molecular targeting of various pathways by sorafenib may enhance the antiproliferative effects of IFN- α , according to Christopher W. Ryan, MD, Oregon Health and Science University, Portland, Oregon. In the SWOG 0412 study median PFS was 7.0 months in the combination arm vs 5.5 months for sorafenib vs 4.7 months for IFN- α . Results from a phase 2 trial of the same combination demonstrated a 36% overall response rate (30% partial, 6% complete). Toxicity with IFN- α , however, may be a limiting factor with this combination and alternative dosing with interferon is needed because of grade 3 and 4 toxicity observed.

Sorafenib and bevacizumab trial. This study hits at the core of much of the rationale underlying combination therapy with antiangiogenic therapy because it addresses whether treatment of the ligand combined with treatment of the receptor will enhance outcomes. According to Jeffrey Sosman, MD, Vanderbilt University Medical Center, Nashville, Tennessee, there is a strong biologic rationale for the combination of the two agents. The concomitant inhibition of the circulating VEGF (with bevacizumab) of VEGFR2 and MAP kinase pathway is hypothesized to enhance the antitumor activity of each agent in RCC (vertical signal blockade). Signal transduction inhibition by sorafenib may result in compensatory increase in VEGF levels. Addition of bevacizumab may prevent resistance that is the consequence of this compensatory mechanism.

In 30 patients, bevacizumab was given every other weekend, sorafenib continuously, with evaluations done every 8 weeks for two cycles of therapy. The combination appeared to significantly increase sorafenib-associated toxicities, predominantly hand-foot syndrome, diffuse rash, functional

stomatitis, anorexia, and fatigue. Hypertension and proteinuria were manageable. At 400 mg bid of sorafenib plus 5 mg/kg of bevacizumab, intolerable toxicities were seen, so full doses of the drugs were not able to be administered.

Clinical activity in RCC was impressive, with few if any progressive disease patients and nearly 50% with partial response and an additional 15% with near partial response. Dr Sosman said that a phase 1 trial is needed to maximize doses and efficacy of both agents before a phase 2 trial can further evaluate maximal VEGFR2 blockade and maximal VEGF blockade.

Combined VEGF pathway inhibition with sunitinib and bevacizumab. Another trial exploring the potential of combining inhibition of multiple aspects of VEGF signaling was covered by Brian Rini, MD. Several hypotheses have been proposed, he said: (1) There is an unopposed increase in VEGF due to effective receptor inhibition, which leads to tumor growth during the “off” period of the sunitinib dosing cycle; (2) VEGF ligand-binding therapy during this time will counteract this increase; and (3) combined inhibition of multiple aspects of VEGF signaling will lead to an increased clinical effect.

A phase 1 study is under way at the Cleveland Clinic to assess use of bevacizumab in combination with sunitinib with the objective of determining the maximum tolerated dose of these agents.

Sunitinib: Update of continuous dosing phase 2 trials. A multi-institutional study is investigating the efficacy and safety of single-agent sunitinib in metastatic RCC when administered in a continuous 37.5 mg/day regimen. The 107 patients were randomized to receive sunitinib in the morning or in the evening at the dose of 37.5 mg per day. The primary endpoint was RECIST-defined objective response rate; secondary endpoint included progression-free survival, adverse events and quality of life measures. Sandy Srinivas, MD, from the Stanford Center reported that continuous dosing was safe and well tolerated. Preliminary results demonstrated a clinical benefit of the regimen with a median PFS of 8.3 months. Levels of three circulating protein biomarkers (VEGF, sVEGFR2, and sVEGFR3) exhibited sustained changes from baseline that were distinct from the cyclical pattern seen with intermittent dosing.

Overview of Combination Data—What's Next?

Robert Motzer, MD, Attending Physician, Memorial Sloan-Kettering Cancer Center, and Professor of Medicine, Weill Medical College of Cornell University

With all of the initiatives examining combination therapy for renal cell carcinoma, what's next? Currently, phase 3 trials have shown a benefit of sunitinib and temsirolimus, specifically in poor risk, over IFN-alpha in first-line therapy, and sorafenib over placebo as a second-line therapy. There are pivotal phase 3 trials that are under way or being conducted for bevacizumab, for pazopanib, and shortly for RAD001, a new mTOR inhibitor. Trials have also recently been initiated to assess combinations, sequences, and comparisons of targeted therapy.

With regard to the types of combinations, the categories include new VHL-targeted therapies with cytotoxic agents, with cytokines, with other VHL-targeted agents, or with agents that interrupt or influence other pathways (Figure 2).

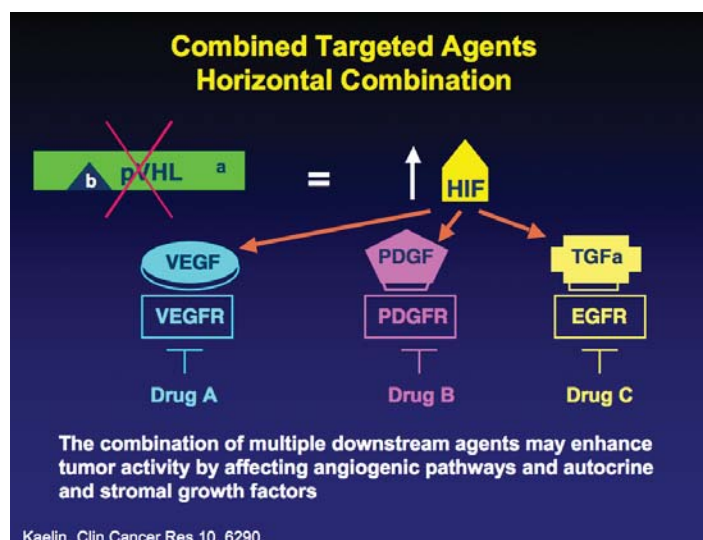


Figure 2.

Cytotoxics. There is not much in the way of new information in renal cancer for the cytotoxics. For the most part, cytotoxics have little role in the treatment of this disease, with the exception of possibly gemcitabine in patients with sarcomatoid variant renal cancer or with undifferentiated tumors. There are some data on sunitinib and gemcitabine from Massachusetts General Hospital, where such combination therapy has been studied. In this combination, investigators have been impressed in terms of the response seen in sarcomatoid renal cancer.

With regard to combinations with targeted drugs and chemotherapy, it is possible that they may find a niche in specific cell types or small groups like sarcomatoid renal cancer, or it may be possible that the activity that we are seeing here is just simply the activity of sunitinib alone. Whether this move continues to show a favorable trend will depend largely on phase 2 data.

Targeted Agents Plus with Cytokines

- **Temsirolimus + IFN** - randomized Phase III
 - Hudes et al – ASCO 2006
- **Bevacizumab plus IFN** - randomized Phase III
 - CALGB (Accrual completed)
 - Roche (Accrual completed)
- **Sorafenib + IFN** - single arm Ph II trials
 - Ryan et al – SWOG S0412
 - Gollub et al – single institution
- **Sunitinib + IFN**
 - Pfizer (Ongoing)
- **IL-2 plus bevacizumab**
 - NCI
 - Chiron/Genentech

Figure 3.

Targeted agents plus cytokines. There is a growing experience in this area: temsirolimus plus interferon, bevacizumab plus interferon. We have seen some encouraging data in terms of sorafenib given in combination with interferon with tolerability and potentially higher response rates. There is an ongoing study with sunitinib plus interferon, a Pfizer-sponsored study that is going on in multiple centers including our own to look at the best dose for sunitinib and cytokine. There are additional studies with bevacizumab plus interleukin-2, given at either high doses or lower doses, that are either ongoing or planned at the NCI as well as company sponsored studies; these trials will give us a better sense of the role of cytokines in addition to targeted therapies, particularly in phase 3 (Figure 3).

Temsirolimus plus interferon. The data are somewhat sobering; pilot data in a phase 1 and phase 2 study suggest encouraging results, but in the phase 3 study it does not appear that the combination is better than interferon, and it appears to be inferior to temsirolimus. Why is this? One possibility is that this particular population of patients, the poor-risk patients, were originally identified through our analysis as a group that does not tolerate cytokine therapy well, and a group for whom cytokine therapy is probably not appropriate, so it may be that this is not the best group to use for assessing the efficacy of cytokine plus combination targeted therapy because of the side effects that they experience. But, the other possibility that we have to examine and take into account when evaluating combination programs and targeted therapy is always the risk that the dose intensity of the drug is sacrificed in the combination. Particularly, if one drug like temsirolimus may have a much higher degree of activity than the interferon, the interferon may just carry with it little or no efficacy and a lot of toxicity. So, it is possible that the combinations, particularly with cytokines or even the other drugs, may not have the same level of efficacy as the single-agent targeted therapies, particularly if we are sacrificing dose. We

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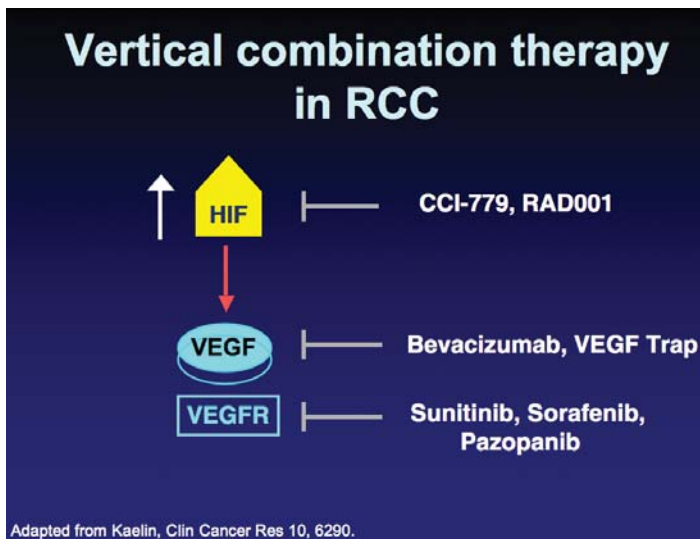


Figure 4. Potential combinations of therapy to achieve inhibition of pathways in RCC.

need to look very cautiously at these combinations and study them in phase 3 trials with these caveats in mind.

Vertical combinations, inhibiting multiple pathways. The interest now is more on the vertical combinations. We have multiple drugs now that have efficacy and that hit the pathway in different places and so the efforts are focusing on combining those drugs in phase 1 and 2 studies (**Figure 4**). However, more data are urgently needed on whether there is improved efficacy along with tolerability for these combinations.

Looking ahead to phase 3 data with combinations. What will be done with these new, exciting combinations as we develop safety data? It is critical from the lessons that we have learned over the last 20 years with cytokines that combinations need to be studied in phase 3 trials. In terms of trial design sunitinib should be the comparator for the first-line randomized phase 3 trial. However, if we are directing

this specifically at the poorest risk patients, then a reasonable standard arm now for comparison would be temsirolimus. On the other hand, if we are examining second-line therapy, then sorafenib would be a very reasonable candidate as a comparator arm to assess these new combinations. We also need to consider stratification factors so that we can make sure that the arms are balanced.

Stratification issues, PFS as primary endpoint. Currently, the best to use are the conventional risk criteria, but these were developed in patients treated with chemotherapy and cytokines, and they may not be entirely predictable with these new targeted therapies. Another direction that we need to take is to look at prognostic factors now to targeted therapies so we can help identify these and interpret our trials. Lastly, with regard to phase 3 studies, a valid endpoint for these is progression-free survival with overall survival being a secondary or other endpoint.

Assessing the pace of research over the last 20 years. Perhaps it is incumbent to look at where we have been and the legacy left by one researcher, one of the pioneers for kidney cancer research, Alan Yagoda, MD, who died in 1995. He was at Memorial Sloan-Kettering Hospital from 1974 to 1989. If not the first person to do studies and clinical trials specifically for kidney cancer, he was certainly one of them. He did one trial after another in his career at Memorial Hospital without any positive response rates. At a seminar that he gave in 1984 about the status of the treatment of kidney cancer, he said, "Results have been universally poor. At this time there appears to be no single agent, hormonal manipulation, or combination drug regimen which is useful in controlling disseminated renal cancer." So, considering that, he would no doubt join us in our amazement at the promise of the new targeted therapies and the progress we have made, and the progress that I am hoping we will continue to make in the next 5 years as we further develop these agents.

Development of Nephron-Sparing and Minimally Invasive Approaches in the Management of RCC

Andrew Novick, MD, Chairman, Glickman Urological Institute, Cleveland Clinic Foundation, and Professor of Surgery, Cleveland Clinic Lerner College of Medicine

There are three approaches today for patients with localized disease: active surveillance being used in an increasing number of our older patients, partial nephrectomy, and radical nephrectomy. Radical nephrectomy remains the most commonly performed procedure for patients with localized renal cell carcinoma, and the major story in recent years has been the incorporation or development of laparoscopic nephrectomy as a standard of care for selected patients, namely those who have T₁ or T₂ renal tumors. Papers such as a study published by Kavoussi et al attest to the long-term efficacy of laparoscopic radical nephrectomy. In this study, comparing open versus laparoscopic nephrectomy for T₁ to T₂ cancers with median follow-up in excess of 6 years in both groups, we see an excellent 5-year and 10-year cancer-specific survival. For patients with more locally advanced disease, those with T_{3a} and T_{3b} tumors, and those requiring lymphadenectomy, I believe that the open technique remains the standard of care, although we are looking at extending the boundaries of laparoscopic surgery in the future.

Where nephron-sparing surgery is concerned, it is clear that we are detecting more and more patients who are candidates. Data from the national cancer database looking at the size of stage I tumors suggest that the stage I tumors that we are detecting are smaller and smaller. They are being detected at an earlier stage, meaning that more of these are eligible for nephron-sparing surgery. However, partial nephrectomy is still being done on a national basis in a relatively small proportion of these cases. A study from the University of Michigan looking at the percentage of surgically treated patients undergoing partial nephrectomy until the end of 2002 shows that it was only 12.3%. I suspect that today, 4 years later, that percentage is higher, but there are still many patients with small T₁ tumors who are having their kidneys removed, suggesting that partial nephrectomy, nephron-sparing surgery, is indeed an underutilized approach.

Extending the Limits of Partial Nephrectomy

There is a clinically relevant need to preserve renal function, and also collectively in some patients who have a normal

opposite kidney. The classic group comprises those with a single tumor less than 4 cm in size. This criterion for an elective partial nephrectomy, based on data from many centers, suggests that the extended oncologic efficacy of partial nephrectomy and radical nephrectomy in this setting is the same, and the reason is because these are small tumors, low-stage tumors. In the instance of occult multicentricity, which is why partial nephrectomy may not always work, the incidence of occult multicentricity is much less with smaller and with low-stage tumors.

This observation has led to the most recent modification of the AJCC TNM staging system where patients with T₁ tumors are now subdivided into those with T_{1a} versus T_{1b}, the aim here to delineate those patients, namely those with T_{1a} tumors who are most suitable for an elective partial nephrectomy with a normal opposite kidney. Now the thinking here concerning elective partial nephrectomy is changing. There are reports from several centers suggesting that partial nephrectomy can be equally well done for patients with T_{1b} tumors, those that are 4-7 cm in size. My own view of this, based on our experience at the Cleveland Clinic, is that this is correct, that it is safe today to extend the limits of elective partial nephrectomy to patients with T_{1b} tumors. These are more technically challenging cases, so the caveat here has to be provided that the surgeons' experience is such that they can optimize the outcome. These patients with larger tumors being selected for elective local resection need to be selected more carefully. I think it is best to limit these cases to more exophytic and less centrally located tumors.

Why are we interested in the concept of elective partial nephrectomy? Because we have learned in recent years that there are advantages, functional and quality of life advantages, to preserving renal tissue, even in patients who have a normal opposite kidney. We have studies from the Cleveland Clinic and others demonstrating that several quality of life parameters are enhanced with preservation of more functioning renal parenchyma. We have several studies demonstrating that unlike our patients who undergo live donor nephrectomy for transplantation in this setting, in a patient with renal cancer, these are older people with comorbid problems that can affect renal function in the future. With these patients there is a benefit to preserving renal function in terms of long-term biochemical renal function and proteinuria. Where nephron-sparing surgery is concerned, we have an enlarging menu of options to choose from.

Where nephron-sparing surgery is concerned, it is clear that we are detecting more and more patients who are candidates. Data from the national cancer database looking at the size of stage I tumors suggest that the stage I tumors that we are detecting are smaller and smaller. They are being detected at an earlier stage, meaning that more of these are eligible for nephron-sparing surgery. However, partial nephrectomy is still being done on a national basis in a relatively small proportion of these cases.

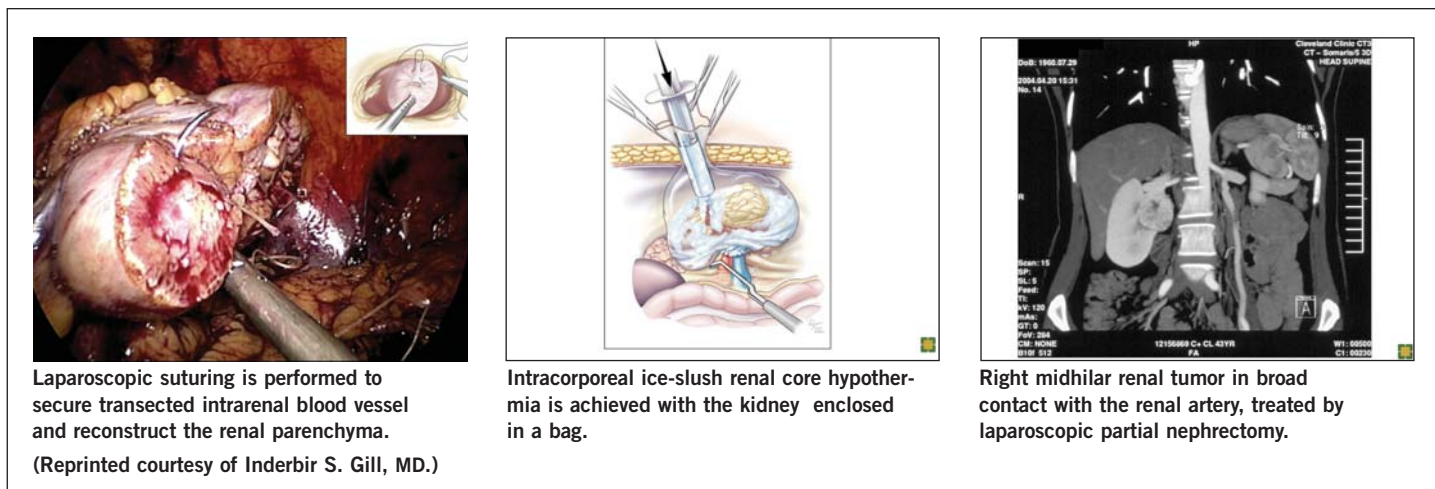


Figure 5.

Open partial nephrectomy is the gold standard. It is the gold standard because it is the technique with which we have had the largest experience, and it is the technique with which we have the longest follow-up. So, we know that this is an approach that works in properly selected cases. More than 2,500 open partial nephrectomies have been performed at the Cleveland Clinic with long-term results in 1,231 patients treated prior to 2002. This experience, along with that of many other centers, has shown that preservation of renal function can be achieved in a very high percentage of these cases, and from an oncologic standpoint extended long term, 10 years or more. Cancer-specific survival is excellent and comparable to that which we can attain with a total nephrectomy. In patients with localized, sporadic renal cell cancer, we have seen recurrent malignancy develop in just under 10% of treated cases. The most challenging cases to treat are those with cancer in a solitary kidney because the implications in terms of preserving or losing renal function are most great when there is only one kidney, and it is the kidney you are operating on. In our series of 400 patients who underwent open partial nephrectomy for localized cancer in a solitary kidney between 1980 and 2002 long-term preservation of renal function was achieved in 95% of these patients, and the cancer-specific survival at 10 years is also satisfactory. So, once again, in the properly selected patient from a biological and oncologic standpoint, this is a good operation.

We have looked at the patterns of tumor recurrence after partial nephrectomy, and it varies directly. It is directly proportional to the pathological stage of the tumor. In a study examining patterns of tumor recurrence in 467 patients, the overall recurrence rate was 9.5%. Local recurrence was only 3.5%. In those with pT₁ and pT₂ renal cell cancer, very few local recurrences occurred, and also a relatively low number of patients developed metastatic disease. The recurrence rate was much higher in those with T₃ disease. The message here is that patients with lower stage disease, those with T₁ to T₂ tumors, do not need to undergo abdominal imaging every 6 months or every year. Our experience has been that repeat imaging every 2 years is sufficient, given the low recurrence rate. In those with T₃ disease we are more vigilant and more

aggressive about imaging for abdominal recurrence.

Patients, however, are at significant risk for an important nephrologic, nononcologic problem. Patients with small remnant kidneys, with reduced renal function, are prone to develop hyperfiltration, renal injury and remnant kidney nephropathy. We demonstrated this in an article published in the *New England Journal of Medicine* quite some time ago. The risk of developing this problem is directly related to the amount of remaining renal tissue and it is a problem that develops over an extended period of time, after 8, 10, and 12 years. This is histopathologically what we are looking at, focal segmental glomerulosclerosis, which is the hallmark of this lesion on renal biopsy. The harbinger of this problem is proteinuria, and so we need to be screening these patients for proteinuria, and considering angiotensin converting enzyme inhibitor therapy in patients who develop proteinuria. It has been shown that this can mitigate the development of this problem.

The New Era of Minimally Invasive Surgery

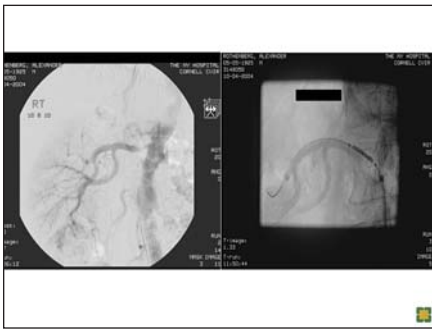
We have entered a new era here, the era of minimally invasive nephron sparing surgery, and we have a number of techniques that are competing with each other to see who will get to the finish line. I think it is fair to say that the most established of these approaches today is laparoscopic partial nephrectomy (Figures 5, 6). It is an advanced laparoscopic surgical technique. There are relatively few surgeons, at least in this country, who have accumulated substantial experience with this approach, and clearly those cases that are most amenable are those patients with a single small tumor or a single small peripheral tumor. This is an ideal case for laparoscopic partial nephrectomy, although the indications are being extended beyond that. The limitations of laparoscopic surgery in this setting are really twofold, and it is not a function of the skill of the surgeon, but of the refinement or sophistication of the instruments that are being used laparoscopically compared to those we use with open surgery. It is more difficult and more cumbersome to achieve hemostasis to prevent bleeding, and it is more difficult to prevent ischemic damage, relatively more difficult than with the open approach.

Laparoscopic vs open partial nephrectomy. Unpublished



A.

A: Solitary right kidney with 5.5 cm infiltrating lower pole tumor. B: The solitary kidney had renal artery stenosis, which was percutaneously stented, and laparoscopic partial nephrectomy was performed 1 month later with excellent outcome. (Reprinted courtesy of Indirbir S. Gill, MD.)



B.

Figure 6.

data from our program involved 1,049 patients who underwent either a laparoscopic or an open partial nephrectomy for a single, localized, sporadic, suspected renal cancer that was less than 7 cm in size, not all of the partial nephrectomies, but just those with a single clinical T₁ renal cancer. There were 595 open and 454 done laparoscopically. This is a retrospective study, so the patients were not matched, and it is not surprising that there were more high-risk patients in the open group, more with comorbid disease, more with symptomatic tumors, many more with solitary kidneys, more with impaired renal function, more with T₁b tumors, and more with central tumors.

In terms of intraoperative data, laparoscopic surgery was associated with about 1 hour less of operating time, but longer renal ischemia time. There were a small number of cases in the laparoscopic group that converted to radical nephrectomy, and a small number converted to open surgery, and we do not consider those to be significant differences. The major finding in the study, and while both approaches were successful in the majority of cases, was the increase in postoperative urologic or renal morbidity with the laparoscopic approach. There were twice as many renal or urologic complications. Most notable among these was postoperative hemorrhage, which occurred in 5.7% of patients in the laparoscopic group, and in only 2% in the open group. There was no significant difference in the incidence of urinary fistulae. A few kidneys were lost in the laparoscopic group, but this was not significant. Another major difference was in the need for a subsequent procedure generally to treat a complication. That occurred about twice as commonly in the laparoscopic group as in the open group.

Oncologic outcomes: open vs laparoscopic group. From the standpoint of oncologic outcome, it is interesting that the diagnosis of renal cancer was made in 84% of patients in the open group and in only 73% in the laparoscopic group. We thought that this was most likely on the basis of tumor size. The tumors in the laparoscopic group were smaller, but in our multivariate analysis controlling for tumor size, the difference still held, so it is not actually clear why cancer is more likely

to be diagnosed in patients who undergo open surgery. There was no significant difference in positive surgical margin rate or in very early 3-year cancer-specific outcome.

Cancer was less likely to be detected with the laparoscopic surgery, and postoperative urological complications, hemorrhage in particular, and the need for a subsequent procedure, were relatively two, three, and four times more likely to occur with laparoscopic surgery. Both of these approaches are successful and effective in most patients, but this is information that we can share with patients who are attracted to minimally invasive surgeries for some very important reasons. However, they need to be

aware that there are some differences between these two approaches. We can conclude that for a single clinical T₁ cancer the laparoscopic approach can yield functional and short-term oncologic outcomes that are equivalent to the open technique associated with longer ischemia time and more postoperative complications. I think the open approach today is certainly the standard for the more complex tumors.

Cryoablation and Radiofrequency Ablation

Patients who have a single small peripheral tumor, particularly older patients with comorbid disease, may be less than ideal candidates for an open or laparoscopic partial nephrectomy. Patients who have undergone a previous renal operation or have developed a local recurrence, for example, after a partial nephrectomy are very high risk for surgery are candidates for ablation. This is a beneficial technique to offer them, and similarly those with severe azotemia, where any form of major intervention on the kidney may push the patient over to dialysis. Ablation may be a safer approach to offer them, but there are issues with these forms of ablation and we really need to keep these in mind and share them with our patients when we discuss them.

We still have much more to learn about controlling the extent of tumor destruction during the procedure. We can do this to some extent with cryoablation. It is much more difficult to do with radiofrequency ablation, namely, to be assured that we have administered all the energy that needs to be administered to completely destroy the tumor. Unlike in partial nephrectomy, we are not taking out a piece of the kidney, giving it to the pathologist, and thereby determining whether it was removed completely, leaving a margin of normal tissue and then determining the stage and the grade. The problem here is that there is no histopathological confirmation of complete tumor destruction and negative surgical margins. So, as we study these forms of ablation we try to infer a successful outcome. How do we infer this? We do it indirectly by looking for loss of contrast enhancement on a follow-up imaging study looking for shrinkage of the treated renal lesion on serial x-rays.

At the Cleveland Clinic we have been biopsying the treated area in these patients at 6 months. We understand all the vagaries of percutaneous biopsies, but we are trying to gather information and learn as much as we can about the outcome here. The ultimate validation here in the absence of tissue for the pathologist can be achieved only by demonstrating in a significant number of these patients that long-term cancer-free survival has been achieved, and we do not have that many patients who have been followed for 5 years or more.

A small group of 60 patients with small tumors have been treated with laparoscopic renal cryoablation, and have been followed for 5 years or more at the Cleveland Clinic. Their median follow-up is 6 years. So far the recurrence rate has been relatively low and the cancer-specific survival rate is good. With cryoablation we have a technique for monitoring intraoperative tumor destruction. This has been studied in preclinical models before we applied it to patients, and it involves the use of intraoperative ultrasound. That distinguishes cryoablation from other techniques.

Radiofrequency ablation is evolving and getting better all the time. The early studies with this were very disconcerting. There were a number of papers suggesting that in patients treated with radiofrequency ablation there was persistent CT tumor enhancement, and even histopathological data showing residual viable tumor. More recent studies are more encouraging. More recent publications on the subject during the last year or two show a higher success rate with success defined as the absence of enhancement on a post-treatment imaging study, and this may be problematic.

The holy grail of tumor ablation is that some day we will

have an approach that allows us to do this extracorporeally, noninvasively, not minimally invasively. The two modalities under evaluation today are high-intensity focused ultrasound and local radiosurgery. Early clinical trials are ongoing, but these early studies have shown viable tumor in surgical specimens in some patients treated with these modalities. Where nephron-sparing ablative therapy for renal tumors is concerned the main problem is adequate intraoperative monitoring of the treated lesion to administer the energy needed for complete tumor destruction. Cryoablation is the most consistently effective approach today. It is the one with which we are beginning to see some long-term data. With RFA, tumor cells are destroyed, but the unreliability of total cell kill is a problem.

As we think about minimally invasive nephron-sparing surgery we really have two options, laparoscopic partial nephrectomy and tumor ablation. The morbidity with laparoscopic partial nephrectomy is going to be somewhat higher. Renal function will be equally well preserved with both, but the oncologic information that we obtain and the oncologic efficacy with laparoscopic partial nephrectomy today is a major advantage over ablative approaches.

Conclusion. When nephron-sparing therapy for renal cancer is considered, open partial nephrectomy is the gold standard based on the established long-term efficacy. Laparoscopic partial nephrectomy in the hands of skilled surgeons is applicable for selected patients, but there remain significant technical limitations; tumor ablation approaches still need to be considered investigational pending longer term outcome data.

Trends to Watch: An Update on Histology, Imaging, Molecular Markers, and Related Topics

Nonconventional Histology

- Overview of Pathology and Molecular Biology
- Surgical Management: Does Histology Enter Into Surgical Planning?
- Role of Cytoreductive Nephrectomy
- Treatment Paradigms for Metastatic Disease

Pathology and Molecular Biology

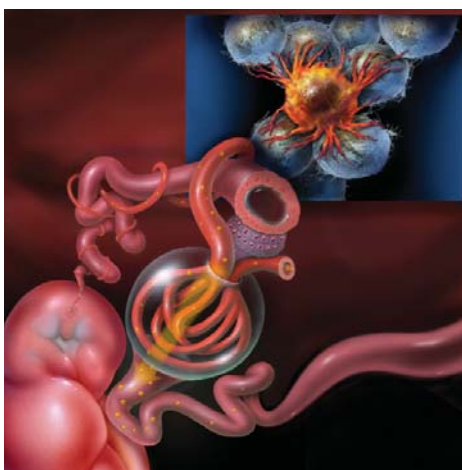
The classification of RCC has undergone numerous changes in the last 20 years, culminating in the classification scheme by the World Health Organization in 2004. Important changes in the new WHO classification include the addition of newer subtypes that have distinct morphologic and/or genetic features, according to Pheroze Tamboli, MB, BS, Associate Professor of Pathology at the University of Texas M.D. Anderson Cancer Center, Houston, Texas.

Papillary. Of all RCC types it is the one most often bilateral and multifocal and associated with papillary adenomas. Papillary RCC is divided into type 1 and type 2; gathering evidence suggests that these two types have distinct clinicopathologic, immunohistochemical, and cytogenetic features, in addition to their morphologic differences.

Chromophobe. This type of RCC accounts for about 5% of all renal carcinomas. There are two morphological variants, typical or classic chromophobe and eosinophilic. There are two types of cells, clear and eosinophilic; both types are usually present with one predominating.

Collecting duct. This type is rare, comprising less than 1% of all RCCs. It is characterized by three features: a tubulo-papillary arrangement of cells; desmoplastic reaction of the stroma; and dysplastic changes in the adjacent collecting ducts. High-grade urothelial carcinoma of the renal pelvis and metastasis to the kidney need to be excluded before a diagnosis of collecting duct RCC can be made.

Renal medullary. This distinctive type of collecting duct RCC has an aggressive clinical course, arises in the renal medulla, and is associated with sickle cell trait.



Xp11. Characterized by translocation of the Xp11 region, these tumors are more common in children and young adults; they comprise about 35% of RCCs affecting the pediatric group.

RCC with sarcomatoid dedifferentiation. Rare, this tumor is seen in only 1% to 2% of RCC. The majority of these lesions are high grade at presentation and the prognosis is very poor. The percentage of the sarcomatoid component has been reported to be important for survival; patients with more than 50% sarcomatoid dedifferentiation in their cancer do poorly.

Does Tumor Histology Enter Into Surgical Planning and Outcomes?

A number of factors now underscore the importance of partial nephrectomy in the management of small renal cortical tumors: an improved understanding of the biology of renal cortical tumors; their diverse tumor histology; varying malignant potential; the relevance of tumor size and stage migration; and studies indicating the efficacy of kidney-sparing surgery. The overzealous use of radical nephrectomy for small renal tumors, by either open or laparoscopic techniques, must now be considered detrimental to the long-term health and safety of the patient with a small renal cortical tumor, said Paul Russo, MD, Attending Surgeon, Department of Surgery, Urology Service, Memorial Sloan-Kettering Cancer Center, New York. Widespread training in partial nephrectomy, either by open or laparoscopic approaches, is clearly indicated in the US and abroad. Urologists seeing a new patient with a small renal mass must consider long-term renal functional preservation, the initiation or worsening of preexisting chronic kidney disease and its subsequent cardiovascular risk enhancement on an equal par with local tumor control and rapid surgical convalescence when counseling the patient.

Cytoreductive Nephrectomy for metastatic RCC in the Presence of Nonconventional Histology

The benefit of cytoreductive nephrectomy with metastatic

RCC of nonconventional histology (papillary, chromophobe, unclassified) is unknown. Christopher G. Wood, MD, of the University of Texas M.D. Anderson Cancer Center, Houston, Texas, reported on results in 89 patients with nonconventional histology who underwent cytoreductive nephrectomy. The results: nonconventional metastatic RCC patients were younger, more likely to have nodal metastases, and more likely to have sarcomatoid differentiation. Median survival for these patients was significantly worse than for patients with conventional metastatic RCC (11.1 vs 19.5 months), even after adjusting for T stage, grade, performance status, age, and sarcomatoid differentiation. Patients with nonconventional histology who had a complete resection of their retroperitoneal nodal metastases with cytoreduction showed a trend toward improved survival, as has been reported in conventional metastatic RCC with nodal disease.

Advances in Imaging for RCC

Several presentations at the symposium highlighted trends in the use of various imaging techniques to detect RCC at an earlier stage. Among the trends:

- A study of the monoclonal antibody G250 for immunophenotyping renal masses using PET suggested that preoperative determination of an aggressive phenotype can guide surgical approaches; antigen down-regulation may indicate response before structural or metabolic indices; and immuno PET combines PET sensitivity with the specificity of antigen targeting.
- Thus, antibody PET with G250 can accurately determine the presence or absence of a clear cell phenotype in renal masses.
- New findings on the use of ultrasound in RCC demonstrate its capability for detecting tumors of various sizes: it detected 75% to 80% of tumors >3 cm, 60% of those 2-3 cm, and 50% of tumors <2 cm.
- In terms of staging for RCC, ultrasound is of limited use for detecting local invasion and nodal metastases and also limited in detecting renal vein involvement. It is useful in detecting IVC involvement. CT remains the gold standard of examination, although MRI is considered useful for vascular invasion. PET-CT is preferred for unsuspected distant metastases.

Keynote Address: the Role of Surgery for Metastatic RCC

Experience from the M.D. Anderson Cancer Center and trials like SWOG 8949 and the EORTC Trial 30947 has helped to clarify guidelines for the use of surgery in metastatic RCC. Recommendations for surgery in this setting emerged from an address by David Swanson, MD, who reviewed the data as he indicated potential situations where surgery appears to be reasonable. He also delineated recommendations compatible with a unified philosophy of management.

Among the highlights of this talk:

- In patients with metastases in multiple organs, nephrectomy should be done but only as part of an integrated strategy. Initial cytoreductive nephrectomy should be done in 85% or more of patients before systemic therapy.

Delayed nephrectomy is advised if initial systemic therapy produces a response or as part of a neoadjuvant therapy protocol.

- Nephrectomy should not be done in “high-risk” patients: those who are poor surgical candidates; grade 4 or sarcomatoid histology; metastases in the liver, brain, or spine.
- All solitary metastases should be resected; adjuvant therapy should be administered only on a protocol.
- Consider initial surgery for limited metastases (1 organ).
- Administer initial therapy for multiple (and some limited) metastases.

Advances in Detection of Molecular Markers and Targets

Identification of key biomarkers in RCC, particularly those that may enhance the effectiveness of cytokine therapy, continue to generate interest and suggest the possibility that these markers could become widely applied as part of the paradigm. For now, however, they are more the focus of investigative work by researchers like Eugene D. Kwon, MD, at the Mayo Clinic Comprehensive Cancer Center. Dr Kwon’s work on B7-H1, a glycoprotein in the B7 ligand family, suggests that elevated expression of B7-H1 may be an indicator for poor prognosis and the need for earlier immunotherapy. This glycoprotein is aberrantly expressed in many cancers and is believed to mediate inhibition of T cells by inducing anergy or apoptosis.

Findings from the Mayo group suggest that blockade of B7-H1 can facilitate T cell-mediated antitumoral responses. For RCC patients, including those with localized tumors, B7-H1 is predictive of increased risk for cancer progression, specific death and overall mortality.

Another area receiving much attention and leading to the development of patient selection models is the use of carbonic anhydrase IX (CAIX) expression. Sabina Signoretti, MD, from the Dana Farber Cancer Center, Boston, reported on her group’s efforts to identify predictors of response. Previously response to IL-2 therapy was significantly associated with clear cell histology with alveolar features and the absence of papillary or significant granular features. Although not yet ready for routine application CAIX expression is considered an important predictor of outcome in RCC patients. A two-compartment model was proposed in which one group of patients with either good pathology or intermediate pathology and high CAIX expression contained 26 of 27 responders compared to only 18 of 39 nonresponders.

More recently efforts have turned toward identifying predictors of response to targeted treatments, including the inhibitor of mTOR (mammalian target of rapamycin) kinase activity, temsirolimus (CCI-779). The Dana Farber researchers have found a positive association of pS6 expression and a trend toward positive expression of pAkt with response to CCI-779. No patients with low expression of these markers experienced an objective tumor response. However, there was no correlation of CAIX, PTEN, and B7-H1 expression or VHL mutational status with response to CCI-779.

Choueiri TK, Rini BI, Garcia J, et al. Clinical prognostic factors in metastatic renal cell carcinoma (RCC) patients treated with anti-VEGF agents.

This study attempted to identify prognostic factors and construct a model predictive for progression-free survival in patients with metastatic RCC receiving anti-VEGF agents. Findings are based on eight prospective clinical trials at the Cleveland Clinic Taussig Cancer Center. Between 2003 and 2006, 124 patients received bevacizumab, sorafenib, sunitinib, or AG-013736 as first- or second-line therapy after cytokine failure. Median PFS was 13.8 months; median follow-up for the 60 patients still progression-free is 8.7 months. Overall, 34% of patients achieved an objective response. Independent adverse prognostic factors for PFS included time from diagnosis to treatment on the current study, baseline platelet, lymphocyte, neutrophil counts, baseline serum calcium, and the number of metastatic sites. Using these six factors, the authors identified two prognostic subgroups: patients with zero to two prognostic factors had a median PFS of 17.6 months (good risk group) compared to only 4 months (poor risk group) in patients with more than two prognostic factors.

Costa LJ, Gonzalez M, Breaker K, et al. Sunitinib malate has activity in advanced RCC previously treated with sorafenib.

Clinical benefits seen with sunitinib and sorafenib are temporary and therapeutic options are needed for RCC refractory to these agents. Differences between these two compounds in terms of targets affected, pharmacokinetics, and toxicity profiles suggest that cross-resistance may not be universal and patients who progressed or were intolerant to one TKI may benefit from treatment with the other. This retrospective analysis evaluated patients who had progressive disease while receiving sorafenib and were subsequently treated with sunitinib. Since January 2006, 13 patients with progressive disease (12) or intolerance (1) to treatment with sorafenib have been treated at the University of Colorado Kidney Cancer Clinic. Performance status was either 1 or 2 and median time to progression with sorafenib had been 24.5 weeks. Ten patients have been evaluated for response, 4 had progressive disease and 6 stable disease as best response. Although none of the patients obtained a response by RECIST criteria, 5 of 10 had evidence of a decrease in tumor measurements. With a median follow-up of 15.3 weeks, median progression-free survival and overall survival were not reached. Toxicity was similar to what has previously been reported with sunitinib. The authors conclude that sunitinib has activity in advanced RCC previously treated with sorafenib.

In the Winter Issue of *Kidney Cancer Journal*

- A report updating you on the importance of IMP3, a potential biomarker to predict metastasis and prognosis in renal cell carcinoma.
- New information on the effect of antivasular and antiangiogenic therapy on the efficacy of radio-frequency ablation in renal tumor models.
- An interview with a leading investigator on an important new clinical trial.
- Why strategies to prolong progression-free survival with combination therapies may be effective.

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