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Renal cell carcinoma (RCC) is considered one of the most malignant tumors in oncology and due to its insidious onset, patients frequently have advanced disease at time of presentation. The mainstay of curative treatment in RCC is surgery—however, a large number of patients (~50%) relapse after nephrectomy. To date hormonal and chemotherapy, both in the adjuvant and metastatic settings, have not shown any impact on survival rates. Until recently, cytokine therapy with IL-2 and/or interferon has been the mainstay of treatment for patients with metastatic RCC. A small percentage of patients (< 10% of the entire population with metastatic RCC) derive major benefits from high-dose IL-2 therapy, achieving long-term, unmaintained remissions. However, the overall low response rate, coupled with the unfavorable side-effect profile, limits the utility of this drug in the majority of patients. Interferon (IFN)-alpha, although somewhat less toxic, has not produced the small percentage of long-term remissions seen with IL-2. Neither drug is effective in the adjuvant setting. Clearly, new treatment options are necessary to fulfill the unmet needs of patients with RCC.

Over recent years, improved understanding of the molecular biology of RCC has defined a number of initial pathways in the proliferation and metastasis of RCC, several of which can potentially be disrupted with currently available targeted agents. The demonstration of antitumor effects with bevacizumab, an anti-vascular endothelial growth factor (VEGF) antibody, validated the importance of the VEGF pathway in the stimulation of angiogenesis in this highly vascularized tumor. In addition to blocking the VEGF receptor, other potentially valid new treatment strategies include: inhibiting VEGF and PDGF receptor tyrosine kinases (i.e., sunitinib), blocking the Raf kinase pathway (sorafenib) or the mTOR pathway (CCI-779).

Recently several novel therapies have become available for the treatment of advanced RCC. Data show that these novel agents are more active than any previous treatment for advanced RCC. Although numerous questions remain unanswered about these agents, many are being addressed in ongoing trials including: Which of these agents is most active? Which targets other than angiogenesis are important? Do any of these drugs have activity after patients progress on another agent with anti-angiogenic activity? Will any of these drugs work in synergy with either chemotherapy or cytokine therapy? These and other questions represent an unfolding story in the evolution of potentially successful novel therapies in a disease for which conventional cytotoxic therapies had little effect. Thus, it is important that clinicians are apprised of new and ongoing studies that show promise with these novel agents.
Learning Objectives

After completing this CME activity, participants should be able to:

- Describe advances in biomarkers and role in developing targeted therapies
- Identify key angiogenic pathways involved in the pathophysiology of RCC
- Critique the results of recently presented trials of novel therapies in RCC
- Review role of adjuvant therapy in RCC

Accreditation Statements

The National Kidney Foundation is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Designation Statement
The National Kidney Foundation designates this educational activity for a maximum of 2.0 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Educational Grantor

This activity is supported by an educational grant from Pfizer Oncology.
Faculty

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Jonathan Rosenberg, MD
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University of California, San Francisco
San Francisco, California

Nizar Tannir, MD, FACP
Assistant Professor
Genitourinary Medical Oncology
MD Anderson Cancer Center
Houston, Texas
Declaration of Disclosure

It is the policy of the National Kidney Foundation to ensure balance, independence, objectivity, and scientific rigor in all CME activities. Faculty participating in this activity are required to disclose to the audience any relationship they may have with the commercial supporters of this activity or with any other commercial organizations whose products or devices may be mentioned in their presentations.

Gary Hudes, MD
  Consultant: Pfizer, Inc., Wyeth Pharmaceuticals, Inc.

Christopher Logothetis, MD
  Speaker's Bureau: Pfizer, Inc., Wyeth Pharmaceuticals, Inc.

Jonathan Rosenberg, MD
  Disclosures will be made on-site.

Nizar Tannir, MD, FACP
Unlabeled/Investigational Use Declaration

During their presentations, faculty may discuss an unlabeled use or an investigational use not approved for a commercial product. Each faculty member is required to disclose this information to the audience when referring to an unlabeled or investigational use.

Gary Hudes, MD
Will be discussing unapproved use of temsirolimus (CCI-779) and AG013736 as well as off-label uses of bevacizumab.

Christopher Logothetis, MD
Has indicated that no unlabeled uses of approved and investigational products will be discussed.

Jonathan Rosenberg, MD
Will be discussing off-label uses of bevacizumab, erlotinib, sorafenib and sunitinib, as well as investigational use of AG-013736 and temsirolimus.

Nizar Tannir, MD, FACP
Will be discussing unapproved use of CG250 monoclonal antibodies, and off-label uses of sorafenib and sunitinib in adjuvant trials.

Disclaimer

The faculty, National Kidney Foundation, and Pfizer Oncology do not recommend the use of any pharmaceutical, diagnostic test, or device outside of the labeled indications as approved by the FDA. Please refer to the official prescribing information for each product for approved indications, contraindications, and warnings.
## Agenda

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<tr>
<th>Time</th>
<th>Session</th>
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<tr>
<td>6:30 – 6:35 am</td>
<td>Welcome &amp; Overview</td>
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<tr>
<td></td>
<td><em>Gary Hudes, MD — Program Chair</em></td>
</tr>
<tr>
<td>6:35 – 7:00 am</td>
<td>Use of Biomarkers and Novel Trial Designs in Developing</td>
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<td></td>
<td>Targeted Therapies for RCC</td>
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<tr>
<td></td>
<td><em>Christopher Logothetis, MD</em></td>
</tr>
<tr>
<td>7:00 – 7:25 am</td>
<td>Molecular Targets in RCC</td>
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<tr>
<td></td>
<td><em>Gary Hudes, MD</em></td>
</tr>
<tr>
<td>7:25 – 7:50 am</td>
<td>Novel Treatments for Advanced Renal Cell Carcinoma</td>
</tr>
<tr>
<td></td>
<td><em>Jonathan Rosenberg, MD</em></td>
</tr>
<tr>
<td>7:50 – 8:15 am</td>
<td>Adjuvant and Pre-Surgical Systemic Therapy for Renal Cell</td>
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<td></td>
<td>Carcinoma</td>
</tr>
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<td></td>
<td><em>Nizar Tannir, MD, FACP</em></td>
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<tr>
<td>8:15 – 8:25 am</td>
<td>Panel Discussion</td>
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<td></td>
<td><em>All Faculty</em></td>
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<tr>
<td>8:25 – 8:30 am</td>
<td>Summary &amp; Conclusions</td>
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<tr>
<td></td>
<td><em>Gary Hudes, MD</em></td>
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</table>
Faculty Biographies

Gary R. Hudes, MD is a graduate of the State University of New York in Brooklyn. He completed his residency in Internal Medicine at The Graduate Hospital in Philadelphia, PA, and earned a fellowship in Hematology-Medical Oncology from Presbyterian-University of Pennsylvania Medical Center, also in Philadelphia.

Dr. Hudes is currently an Attending Physician and Director of the Genitourinary Malignancies Program at Fox Chase Cancer Center in Philadelphia. He holds board certification in Internal Medicine, Hematology, and Medical Oncology.

Dr. Hudes is a member of the American College of Physicians, American Association for the Advancement of Science, American Society of Clinical Oncology, American Association for Cancer Research, and Pennsylvania Oncologic Society. He also actively participates in numerous national committees, including the National Cancer Institute Clinical Therapy Evaluation Program Concept Review Committee, the Radiation Therapy Oncology Group (RTOG) Data Monitoring Committee, the Eastern Cooperative Oncology Group Genitourinary Core Committee, the American Association for Cancer Research Investigational Agents Subcommittee, and the National Comprehensive Cancer Network Kidney/Testicular Cancer Guidelines Panel, Bladder Cancer Guidelines Committee, and Clinical Trials Advisory Committee.

Dr. Hudes has clinical and research interests in prostate cancer and developmental therapeutics. He is a participant in several ongoing trials, acting as Co-director in a US Department of Defense study on prostate cancer survivors with rising PSA and their spouses, a National Institutes of Health study on the identification and analysis of a genetic susceptibility to testicular cancer, and a Fox Chase Cancer Center translational research trial on expression profiling in metastatic prostate cancer.

Dr. Hudes has lectured around the country and serves on the editorial boards of Investigational New Drugs and Clinical Prostate Cancer. In addition, he has authored over 150 abstracts, book chapters, and original articles, which have been published in journals such as American Journal of Clinical Oncology, Journal of Clinical Oncology, Investigational New Drugs, Urology, Cancer, Oncology, Clinical Cancer Research, Drugs and Aging, The Urologics Clinics of North America, and Cancer Immunology Immunotherapy.
Faculty Biographies

Christopher Logothetis, MD obtained his medical degree at the University of Athens School of Medicine in Greece. He completed his internship and residency in Medicine at Cook County Hospital in Chicago, Illinois, and his fellowship in Medical Oncology at The University of Texas (UT) M. D. Anderson Cancer Center in Houston. Dr. Logothetis is board-certified in both Internal Medicine and Medical Oncology.

Dr. Logothetis is presently Professor and Chairman of the Department of Genitourinary Medical Oncology at UT M. D. Anderson Cancer Center. He is also Director of the Genitourinary Cancer Center and the Prostate Cancer Research Program, which are multidisciplinary collaborations of physicians and scientists dedicated to genitourinary cancer treatment, research, prevention, and education.

Among other responsibilities, Dr. Logothetis is a leader in the Prostate Cancer Foundation’s Therapy Consortium, an active group of researchers involved in the development of innovative therapy for prostate cancer. The primary focus of his research has been prostatic carcinomas and their treatment. Dr. Logothetis is credited with validating clinical biologic markers for prostate cancer and developing specific gene therapy approaches for prostatic carcinoma. He is currently involved in a trial of preoperative $p53$ gene therapy, which has elucidated the specific function of the c-cell adhesion molecule. Dr. Logothetis also directs an important phase III trial in which a 4-drug regimen plus androgen ablation will be compared with androgen ablation alone as the initial treatment for nonlocalized prostate cancer.

Dr. Logothetis recently was invited by the National Institutes of Health (NIH) to discuss the “Biological Basis for the Development and Application of Therapy for Prostate Cancer.” At NIH, he presented prepublication data from several ongoing clinical trials, and emphasized his team’s integrative strategy for analyzing the basic biology of prostate cancer and translating this into improved disease diagnosis and treatment.

Dr. Logothetis has authored over 200 peer-reviewed publications, the most recent of which have appeared in the *Journal of Clinical Oncology*, *Oncogene, Journal of Urology, Cancer Research, Clinical Cancer Research, Anticancer Research, Cancer Epidemiology, Biomarkers, and Prevention, Neoplasia*, and *Nature Reviews in Cancer*. 


Faculty Biographies

Jonathan Rosenberg, MD is a graduate of Harvard Medical School in Boston, Massachusetts. He completed his internship and residency in Internal Medicine at Cornell University in Ithaca, NY. He then earned a fellowship in Hematology/Oncology at the University of California, San Francisco (UCSF).

At present, Dr. Rothenberg is an Assistant Professor in the Division of Hematology/Oncology and a member of the Prostate Cancer Fellowship Program at UCSF. He is the recipient of numerous honors, including the Duke University Horn Biology Prize, the David E. Rogers Research Prize Finalist from Cornell University Department of Medicine, the UCSF Division of Hematology/Oncology Amgen Fellowship, and the American Association for Cancer Research Conference Best Poster.

Dr. Rothenberg’s main research interest is on the genetics of prostate cancer. In particular, he has focused on the mapping and trapping the chromosome 19q glioma tumor suppressor gene. He is currently the Protocol Chair for a National Cancer Institute-funded phase II study on ixabepilone compared with mitoxantrone and prednisone in treating patients with refractory metastatic prostate cancer.

Complementing his research endeavors, Dr. Rosenberg has authored a number of book chapters and several journal articles and abstracts, which have been published in Cancer Research, Proceedings of the American Society for Cancer Research, Oncogene, Journal of Neuropathology and Experimental Neurology, and Current Opinions in Oncology.
Faculty Biographies

Nizar M. Tannir, MD, FACP received his training in medicine at the American University of Beirut in Lebanon, where he also completed his internship and residency. He then earned a fellowship in Medical Oncology from the University of Texas (UT) M.D. Anderson Hospital and Tumor Institute in Houston, followed by a fellowship in Hematology from the University of Medicine and Dentistry of New Jersey in Newark. Dr. Tannir is also a Clinical Fellow in the Department of Leukemia at UT M.D. Anderson Cancer Center.

Currently, Dr. Tannir holds board certification from the American Board of Internal Medicine, American Board of Internal Medicine/Hematology, and American Board of Internal Medicine/Medical Oncology. His present position is Assistant Professor in the Department of Genitourinary Medical Oncology of the Division of Cancer Medicine at UT M.D. Anderson Cancer Center. Previously, he was the Director of the Kentucky Cancer Clinic in Hazard, and served as Voluntary Faculty at the University of Kentucky in Lexington. Dr. Tannir is a member of American Society of Clinical Oncology, American Association Cancer Research, and National Arab American Medical Association. He is also Faculty Senator for Genitourinary Medical Oncology at UT M.D. Anderson Cancer Center.

Dr. Tannir has clinical and research interests in biology and the treatment of renal cell and prostate cancers. He has participated in several phase II clinical trials, evaluating such novel agents as capecitabine plus gemcitabine in patients with advanced renal cell cancer previously treated with immunotherapy; ABT-510 in subjects with advanced renal cell carcinoma; interferon alfa alone, CCI-779 alone, and the combination of interferon alfa and CCI-779 in first-line poor-prognosis subjects with advanced renal cell carcinoma; pemetrexed and gemcitabine in cisplatin refractory germ cell tumor; and SU11248 as first-line therapy in patients with advanced non-clear cell renal cell cancer.

Dr. Tannir has written numerous peer-reviewed articles, book chapters, letters, and abstracts that have appeared in journals such as *Antimicrobial Agents and Chemotherapy*, *Clinical Chemistry*, *Cancer, Journal Clinical Oncology*, *European Journal of Cancer and Clinical Oncology*, *Leukemia & Lymphoma*, and *The Journal of Urology*. In addition, he has lectured extensively at both national and international events on a variety of topics pertaining to adjuvant strategies in renal cell cancer, management of advanced renal cell carcinoma, strategies for prostate cancer prevention, and recent advances in the diagnosis and management of genitourinary cancers.
With advances in the understanding of molecular pathophysiology of cancer cells, an increasing number of therapeutic agents targeting various components of tumorigenesis pathways have been identified. In the case of renal cell carcinoma, anti-angiogenic agents targeting the vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) signaling system have been developed.

Although these recent novel anti-angiogenic therapies were developed as a result of the insights gained with regards to RCC molecular biology, most current clinical trials of targeted therapy have not been designed to validate mechanistic hypotheses. Rather, clinical trials are often designed using empiric combinations or sequences of agents, when in fact, a rationally-designed study based on molecular pathways or mechanisms of action should be employed. To facilitate translating preclinical scientific observations to clinical research and practice, pre- and post- surgical tumor samples obtained in the neoadjuvant setting can be used to confirm biologic activity in vivo and correlate it with clinical endpoints.

Continued research in the use of biomarkers and rational trial design will identify biological determinants of response and resistance, characterize responder phenotype, and define appropriate therapeutic strategy. This presentation will review the strategies and currently ongoing trials to identify rational use of therapeutic agents in RCC.
Advances in Targeted Molecular Therapies for RCC

Christopher Logothetis, MD
MD Anderson Cancer Center
Houston, TX

LANDSCAPE IN RENAL CELL CARCINOMA CHANGED

- Current State of therapy
- Integrated Therapy Development strategy
The Challenge
(Overcoming “Cytotoxic Paradigm”)

Recent therapies result from new insights into RCC molecular biology, yet most current studies are not designed to validate mechanistic hypotheses.

Preoperative Model
Interface with Therapy & Biology

Linking tumor biology to clinical observations will lead to individualized therapy for subsets of patients

Eric Jonasch
**MDACC Bevacizumab-Erlotinib Trial**

- Bevacizumab 10mg/kg IV Q14 days
- Erlotinib 150mg PO QD For 8 weeks

**Response**
- Or Stable
- Progressive, Good PS
- Progressive, Poor PS

**Nephrectomy,**
- Continue Same Agents
- New Chemo, Or Best Supportive Care

**Progressive,**
- Poor PS

**New Chemo,**
- Nephrectomy,
- Continue Same Agents

**Response**
- Or Stable
- Progressive, Good PS

**Stable/Respond,**
- Continue Sorafenib

**Progression:**
- New Chemo

---

**MDACC Sorafenib Presurgical Trial**

- Sorafenib 400mg By mouth BID

**Nephrectomy,**
- Then 10 wks Sorafenib
- Then 9 wks Sorafenib

**1 wk Sorafenib,**
- Nephrectomy,
- Then 9 wks Sorafenib

**4 wks Sorafenib,**
- Nephrectomy,
- Then 6 wks Sorafenib

**Stable/Respond,**
- Continue Sorafenib

**Progression:**
- New Chemo

---

**Renal Cell Carcinoma Applied Research (MD Anderson Cancer Center)**

- Defining Relevant Clinical Readouts
- Defining Relevant Biological Readouts

- Infrastructure

---
Preop Studies

- No prior systemic therapy
- Primary in place
- Conventional histology
- Performance status of 0 or 1

Targeted Agents in Phase III
(Are we asking the right question!)

- Second-line: Sorafenib vs Placebo
- First-line: Bevacizumab + IFN vs IFN
- First-line: Sunitinib vs IFN
- First-line poor-risk: Temsirolimus vs IFN vs Temsirolimus + IFN
From Drug to Therapy Development (Phase II dilemma)

- IFN, IL-2 and 5-FU in RCC-Phase II Studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>RR%</th>
<th>CR%</th>
<th>PR%</th>
<th>Med.Survival</th>
</tr>
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<tr>
<td>Hanninen</td>
<td>1996</td>
<td>120</td>
<td>39</td>
<td>11</td>
<td>28</td>
<td>Not reached</td>
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<tr>
<td>Ellerhorst</td>
<td>1997</td>
<td>55</td>
<td>31</td>
<td>8</td>
<td>22</td>
<td>23 months</td>
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<tr>
<td>Tourani</td>
<td>1998</td>
<td>62</td>
<td>19</td>
<td>1.6</td>
<td>17.7</td>
<td>2yr surv. 33%</td>
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<td>Dutcher</td>
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<td>50</td>
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<td>17.5 months</td>
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<td>Van Herpen</td>
<td>2000</td>
<td>52</td>
<td>12</td>
<td>0</td>
<td>12</td>
<td>16.5 months</td>
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From Drug to Therapy Development (Phase II dilemma)

- Phase III Trial: Negrier et al, 2000

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<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>RR</th>
<th>CR</th>
<th>PR</th>
<th>Survival (Mo)</th>
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<tbody>
<tr>
<td>SC IL2 &amp; IFN</td>
<td>70</td>
<td>1.4</td>
<td>0</td>
<td>1.4</td>
<td>13</td>
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<tr>
<td>SC IL2 &amp; IFN</td>
<td>61</td>
<td>8.2</td>
<td>0</td>
<td>8.2</td>
<td>13</td>
</tr>
<tr>
<td>+ 5FU</td>
<td></td>
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Questions in Developing a Therapeutic Strategy for MRCC

- Do various “targeted agents” modulate the same phenotype?
- What is the “responsive phenotype”?
- Are there qualitative differences among various “targeted agents” with respect to efficacy and toxicity?
Phase II Trial with Sequential Randomization Among Four Targeted Agents in Metastatic Renal Cell Cancer (MRCC)

Nizar M. Tannir

Clinical Dilemmas Toward Rational Combinations

- Which is the most effective “targeted agent” given up-front?
- Which is the most effective “targeted agent” given in second-line setting?
- What is the optimum two-stage sequence of “targeted agents”?
- Toxicity of combination(s)?

Study Endpoints

Primary
- Rank the individual agents by time to first progression (TTP1)
- Rank the individual agents by time to second progression (TTP2)
- Rank the two-agent treatment sequences by total time (TTP1+TTP2)
**Study Endpoints**

Secondary
- Establish tissue repository to perform hypotheses generating studies of serially assessed candidate markers of response
- Relate tumor characteristics to primary & secondary objectives

**Treatment Schema**

<table>
<thead>
<tr>
<th>TTP1</th>
<th>TTP2</th>
</tr>
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<tbody>
<tr>
<td>Bevacizumab</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Temsirolimus</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Sunitinib</td>
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</table>

Randomization 1:1:1:1

MSKCC Stratification

**Comparison of Twelve Sequences**

<table>
<thead>
<tr>
<th>Beva</th>
<th>Temsi</th>
<th>Soraf</th>
<th>Suniti</th>
</tr>
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<tr>
<td>Beva</td>
<td>Temsi</td>
<td>Soraf</td>
<td>Suniti</td>
</tr>
<tr>
<td>Beva</td>
<td>Soraf</td>
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<td>Suniti</td>
</tr>
<tr>
<td>Beva</td>
<td>Suniti</td>
<td>Temsi</td>
<td>Soraf</td>
</tr>
<tr>
<td>Suniti</td>
<td>Temsi</td>
<td>Soraf</td>
<td>Beva</td>
</tr>
<tr>
<td>Suniti</td>
<td>Soraf</td>
<td>Temsi</td>
<td>Beva</td>
</tr>
<tr>
<td>Suniti</td>
<td>Beva</td>
<td>Temsi</td>
<td>Soraf</td>
</tr>
</tbody>
</table>
Statistics

- Maximum number of patients = 240
- Anticipated accrual = 6-12 patients/mo
- Interim analysis: if an initial agent is dropped, then patients are randomized initially among the remaining agents; likewise if a sequence is dropped then all 1st and 2nd randomizations are adjusted accordingly

Background - Origin of Mature CECs

Normal blood vessels
- Minimally dependent on cell survival factors
- Low permeability
- Pericytes present
- Low integrin expression

Tumor blood vessels
- Growth and survival factors (e.g., VEGF) present
- Highly permeable
- Fewer pericytes
- Upregulation of integrins

Background - Mobilization of CEPs

Sinusoidal vessels
- VEGF-A
- PIGF
- bFGF
- Angiopoietins
- SDF-1
- HIF-1
- PDGF
- Epo
- G/GM-CSF
- Statins
- Ginkgo biloba

Bone marrow
- Recruitment
- HSC
- EPC
- MMP-9
- VEGF
- PI GF
- PIGF
- bFGF
- Angiopoietins
- SDF-1
- HIF-1
- PDGF
- Epo
- G/GM-CSF
- Statins
- Ginkgo biloba

Modified from Raji et al. Nature Rev Cancer 2002
Timing and Integration Into Ongoing Clinical Trials – Renal Ca

GENERAL
Nephrectomy
Pre 4-6 w 3 mo

Bevacizumab
Nephrectomy
Baseline 2 w Pre 4-6 w 3 mo 5 mo … PRO

METASTATIC - Neoadjuvant Bevacizumab

Towards a Therapy Strategy

Key goals in the next few years:

1. Investigate biological determinants of response and resistance.
2. Characterize responder phenotype.
3. Define utility of defined therapeutic strategies as a function of tumor biology, drug pharmacology, and pharmacogenomics.
Renal cell carcinoma (RCC) is a heterogeneous group of diseases, each characterized by distinct histology, natural history, and response to therapy. The clear cell histology subtype represents 75-85% of all RCCs. At diagnosis, approximately 25% to 30% of RCC patients have advanced (metastatic) disease, for whom treatment options were very limited until recently.

Within the last decade, better understanding of the molecular pathogenesis RCC has resulted in the identification of several targets for treatment. The von Hippel-Lindau tumor suppressor gene (VHL), in normal conditions, produces the VHL protein that targets hypoxia inducible factor (HIF) for degradation. HIFs are important in regulating response to hypoxia, leading to transcription and expression of numerous proteins including vascular endothelial growth factors (VEGF) and platelet derived growth factors (PDGF).

Inactivation of VHL through mutation or methylation results in accumulation of HIF despite normal tissue oxygenation, leading to overexpression of VEGF and PDGF, which results in tumor angiogenesis and proliferation. This lecture will review various targets of the angiogenesis pathway that have been evaluated for clinical development including antibodies, and small molecular therapy.
Molecular Targets in Renal Cell Carcinoma

Gary Hudes
Fox Chase Cancer Center
Philadelphia, PA

Epidemiology of RCC

- Incidence: ~36,000 new cases of kidney renal cell carcinoma (RCC) in the United States
- Mortality: Each year ~13,000 patients will die
- RCC accounts for ~90% of all kidney tumors
- Most frequently diagnosed in people aged 50–70 years
- Smoking and obesity are known risk factors

RCC = renal cell carcinoma.


Clinical Staging and Prognosis in RCC: American Joint Committee on Cancer Criteria

Stage I
Tumor <7 cm in greatest dimension and limited to kidney; 5-year survival, ~95%

Stage II
Tumor >7 cm in greatest dimension and limited to kidney; 5-year survival, ~88%

Stage III
Tumor in major veins or adrenal gland, tumor within Gerota's fascia, or 1 regional lymph node involved; 5-year survival, ~59%

Stage IV
Tumor beyond Gerota's fascia or >1 regional lymph node involved; 5-year survival, ~20%
**Metastatic RCC Prognosis: Memorial Sloan-Kettering Risk-Factor Model**

Greater number of risk factors is associated with worse prognosis*

- 0 risk factors (164 patients, 30 alive)
- 1 or 2 risk factors (348 patients, 23 alive)
- 3, 4, or 5 risk factors (144 patients, 1 alive)

*Risk factors: no prior nephrectomy, KPS <80, low HGB, high corrected calcium, high LDH.

HGB=hemoglobin; KPS=Karnofsky performance status; LDH=lactate dehydrogenase.


**High-Dose IL-2 vs IL-2 Plus IFN-α in mRCC: Overall Survival**

Median survival (months)

- High-dose IL-2 (n=96) 17
- IL-2 + IFN (n=96) 13

\( P = .211 \)


**Meta-analysis of IFN-α in mRCC**

One-year survival

<table>
<thead>
<tr>
<th>Study</th>
<th>n/N</th>
<th>Control n/N</th>
<th>Data ratio</th>
<th>Odds ratio 95% CI</th>
<th>Weight</th>
<th>Odds ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krämer 1995</td>
<td>14/35</td>
<td>20/28</td>
<td>9.8</td>
<td>0.27 (0.09-0.77)</td>
<td>9.6</td>
<td>0.27 (0.09-0.77)</td>
</tr>
<tr>
<td>MRCRC 2000</td>
<td>99/167</td>
<td>114/168</td>
<td>54.8</td>
<td>0.63 (0.40-0.98)</td>
<td>26.9</td>
<td>0.63 (0.40-0.98)</td>
</tr>
<tr>
<td>Pytonen 1999</td>
<td>35/79</td>
<td>46/78</td>
<td>26.9</td>
<td>0.50 (0.26-0.94)</td>
<td>8.6</td>
<td>0.50 (0.26-0.94)</td>
</tr>
<tr>
<td>Saltmarch 1990</td>
<td>21/30</td>
<td>20/30</td>
<td>8.6</td>
<td>0.85 (0.28-2.61)</td>
<td>8.6</td>
<td>0.85 (0.28-2.61)</td>
</tr>
<tr>
<td>Total (85% CI)</td>
<td>311</td>
<td>304</td>
<td>100.0</td>
<td>0.56 (0.40-0.77)</td>
<td>1.0</td>
<td>0.56 (0.40-0.77)</td>
</tr>
</tbody>
</table>

Immunotherapy in mRCC: PERCY Quattro Study Design

Randomization (N=492 mRCC patients)

- Metyrapone-progesterone acetate (MPA) 200 mg/day (oral) (n=123)
- IFN SC 9 million U 3 days/week (n=122)
- Medroxyprogesterone acetate (MPA) 200 mg/day (oral) (n=123)
- IL-2 SC 18 million U 5 days/week for 2 cycles of 4 weeks (n=125)
- IL-2+ IFN ID IL-2 + IFN 6 million U 3 days/week (n=122)

Evaluation at 12 weeks

- Progression → CR, PR, or SD → Stop → 3 additional months

* Primary end point: Overall survival

Negrier S et al. Paper presented at: ASCO; May 13-17, 2005; Orlando, FL.

PERCY Quattro Trial in mRCC: Overall Survival

- MPA Median 14.9 months
- IFN Median 15.2 months
- IL-2 Median 15.3 months
- IL-2+IFN Median 16.8 months

Negrier S et al. Paper presented at: ASCO; May 13-17, 2005; Orlando, FL.

Summary of RCC Management

- Surgery is the only curative option for patients with early RCC (T1–T2)
  - Recurrence rates are high for patients with locally advanced RCC (T3)
- mRCC is generally resistant to standard chemotherapy
- Pre-2006: 2% to 3% of patients with RCC received FDA approved cytokine therapy
  - Interferon used most often
- 2006: Sunitinib and Sorafenib approved for advanced RCC
- 2006 and beyond: New agents and combinations

Hudes - Molecular Targets in RCC
**RCC Is a Highly Vascular Tumor**


**Angiogenesis**

- The formation of new blood vessels from pre-existing vasculature
  - Angiogenesis facilitates tumor growth and metastasis
  - Therapeutic inhibition of tumor angiogenesis should be effective in selected solid malignancies
  - Target tissue is in direct contact with blood, facilitating drug delivery
  - Genetically stable endothelial cells may be less prone to genetic aberrations and the development of drug resistance than tumor cells
  - Toxicity to other normal tissues is expected to be low

**Angiogenesis Stimulatory and Inhibitory Factors**

- **PROANGIOGENIC**
  - Acidic and basic FGF
  - Angiopoietin-1
  - Hepatocyte growth factor
  - Interleukin-8
  - Placenta growth factor
  - PDGF
  - TGF α and β
  - TNF-α
  - VEGF

- **ANTIANGIOGENIC**
  - aaATIII
  - Angiopoietin-2
  - Angiostatin
  - Endostatin
  - Histidine-rich glycoprotein
  - Interferon-α, -β, -ϒ
  - Platelet factor-4
  - Prolactin fragment
  - Thrombospondin-1 and -2
  - TIMPs 1, 2, and 3
VEGF is a Key Pro-Angiogenic Factor

VEGF is directly implicated in endothelial cell adhesion, proliferation, and migration.

VEGF is directly implicated in proteolytic destruction of the ECM.

VEGF is directly involved in capillary tube formation.

The VEGF Family of Growth Factors

• VEGF-A: most potent direct-acting angiogenic protein. Expression leads to endothelial cell proliferation, angiogenesis, and increased vascular permeability.
• VEGF-B: structurally closely related to VEGF-A, very stable and not upregulated by factors that induce expression of VEGF-A.
• VEGF-C and VEGF-D: regulate the growth of lymphatic vessels.

VEGF Receptors

• VEGF-1 (Flt-1): high-affinity receptor for VEGF-A, VEGF-B, and PIGF.
• VEGF-2 (KDR/Flik-1): high-affinity receptor for VEGF-C, VEGF-D, and VEGF-E; major mediator of physiologic and pathologic effects of VEGF-A on vascular endothelial cells.
• VEGF-3 (Flt-4): high-affinity receptor for VEGF-C and VEGF-D; major signaling pathway for lymphangiogenesis.
**VEGFR/PDGFR: Roles in Angiogenesis**


---

**Histological Classification of Epithelial Neoplasms of the Kidney**

<table>
<thead>
<tr>
<th>Type</th>
<th>Associated mutations</th>
<th>Incidence (%)</th>
<th>Locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>VHL</td>
<td>75</td>
<td>3p25</td>
</tr>
<tr>
<td>Papillary type 1</td>
<td>c-Met</td>
<td>5</td>
<td>7q31</td>
</tr>
<tr>
<td>Papillary type 2</td>
<td>FH</td>
<td>10</td>
<td>1q42</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>BHD</td>
<td>5</td>
<td>17p11</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>BHD</td>
<td>5</td>
<td>17p11</td>
</tr>
</tbody>
</table>

BHD=Birt-Hogg-Dubé; FH=fumarate hydratase; VHL=von Hippel-Lindau.

---

**VHL, Hypoxia, and RCC Tumorigenesis**

\[
\begin{align*}
\text{HIF1-\(\alpha\)} & \quad \xrightarrow{\text{VHL}} \\
\text{HIF DEGRADATION} & \\
\text{HYPOXIA or VHL loss} & \\
\text{TARGET GENE INDUCTION} & \\
\text{GLUT-1} & \quad \text{VEGF} \\
\text{Glucose transport} & \quad \text{Angiogenesis} \\
\text{IGF} & \quad \text{CAIX} \\
\text{Growth/survival} & \quad \text{Metabolism/pH regulation} \\
\text{CXCR4} & \quad \text{Metastasis/Proliferation/Survival}
\end{align*}
\]

HIFα in Renal Cell Carcinoma

- 66 clear cell tumors analyzed (Western blots)
- Levels of expression were correlated with a variety of clinical & pathologic variables
- No correlation with stage, grade, tumor size, or DNA ploidy
- Survival analysis demonstrated significant association of high HIFα and survival (p<0.024)

<table>
<thead>
<tr>
<th>↑ HIFα</th>
<th>No.</th>
<th>↓ HIFα</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival (yrs)</td>
<td>≈1.0 yr.</td>
<td>44</td>
<td>≈8.0 yrs.</td>
</tr>
</tbody>
</table>

- In multivariate analysis stage and HIFα were independent prognostic factors.

Lidgren et al, Clin Can Res, 2005
**VEGF/PDGF : Clear Cell RCC**

- VEGF : serum levels ↑, correlation with poor prognosis
- VEGF expression - RCC tumors :
  - mRNA ↑ 3-13 fold (Takahashi 1994)
  - protein (IMH) ↑ 3-37 fold (Nicol 1997)
- PDGF expression :
  - mRNA and protein present (Xu 2005)
- PDGFβ : mRNA expressed in RCC cell lines (Xu 2005)

**Approaches to the Inhibition of VEGF Signaling**

![Diagram of VEGF signaling inhibitors]

**Angiogenesis Inhibitors**

- Bevacizumab
- Sunitinib
- Sorafenib
- AG013736
- Temsirolimus (CCI-779)

…and more in development
Epithelial Cancers Overexpress EGF Receptor

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>% Overexpressing EGF Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>70-90%</td>
</tr>
<tr>
<td>Prostate</td>
<td>80-90%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>60-80%</td>
</tr>
<tr>
<td>Breast</td>
<td>20-30%</td>
</tr>
<tr>
<td>NSCL</td>
<td>60-80%</td>
</tr>
<tr>
<td>Esophageal</td>
<td>60-80%</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>50-90%</td>
</tr>
</tbody>
</table>

VEGF and EGFR Inhibition: Rationale

- Mechanisms of interaction:
  - ↑ EGFR expression - associated with increased VEGF production (Ciardiello et al., 2000)
  - EGFR activation induces (Sini et al., 2005)
    - Proliferation endothelial & tumor cells
    - VEGF release
  - Acquired resistance to EGFR inhibitors in part mediated by VEGF associated angiogenesis (Viloria-Petit et al., 2001)
- Preclinical models - additive / synergistic inhibition of tumor growth

mTOR: The Mammalian Target of Rapamycin

- A 256 kDa protein kinase also a.k.a. FRAP, RAFT-6
- Member of the PI3-related kinase family
- Functions as a signal integrator: detects nutrient availability, oxygen/pH state, and growth factor binding signals
- Part of a signaling pathway that regulates the translation of specific mRNA involved in G1-S transition (e.g., cyclin D1, c-myc) and angiogenesis
mTOR Signaling
Relevance to Human Tumors

- PTEN loss
- Glioblastoma
- Endometrial cancer
- Prostate cancer
- PI3K/Akt activation
- Her2+ Breast Ca
- CML (Bcr-Abl)
- Ovarian cancer (gene amplification)

- TSC1/2 loss
- Tuberosus Sclerosis
- Renal angiomyolipomas (TSC2 mut)
- Pulmonary lymphangiomylomatosis

- PTEN loss
- Glioblastoma
- Endometrial cancer
- Prostate cancer

- TSC1/TSC2
- Rheb
- PI3K
- Akt

- S6K
- 4EBP1
- Translation

- HIF overexpression
- Renal carcinoma (VHL loss)

- Cyclin D1, dMyc, HIF1α, and others

- mTOR
- p70 S6K

- Cyclin D1 overexpression
- Mantle cell lymphoma
- Breast cancer

- Myc overexpression
- Burkitts lymphoma

- CCI-779 (Temsirolimus, Wyeth)
  - Phase II single agent and combinations, phase III renal carcinoma, breast cancer
  - IV and oral formulations

- CCI-779 (Temsirolimus, Wyeth)
  - Approved for immunosuppression, transplant (daily oral schedule)

- RAD001 (Everolimus, Novartis)
  - Approved for immunosuppression/transplant (daily oral schedule)
  - Phase I-II cancer trials of oral formulation, combination studies

- AP23573 (Ariad)
  - Phase I, IV formulation

mTOR Regulates Translation Initiation

- Translational Initiation and Cell Growth

mTOR Inhibitors in the Clinic

- Sirolimus (Rapimmune)
  - Approved for immunosuppression, transplant (daily oral schedule)

- CCI-779 (Temsirolimus, Wyeth)
  - Approved for immunosuppression, transplant (daily oral schedule)

- RAD001 (Everolimus, Novartis)
  - Approved for immunosuppression/transplant (daily oral schedule)

- AP23573 (Ariad)
  - Phase I, IV formulation
mTOR Signaling Complexes: Effects of Rapamycin on HIF-α Translation

Effect of CCI-779 on VEGF Production in A498 Cells in Vitro

Provided by J Gibbons, Wyeth Research.

mTOR Inhibition and other Targets in Renal Carcinoma

- Cytokines
- VEGF/VEGFR
- Rheb (farnesylated protein)
- IGF/IGFR
- PKC

From Choo and Blenis, Cancer Cell, 2006

Provided by J Gibbons, Wyeth Research.
Effect of 4 weekly cycles of CCI-779 and Interferon-alpha on growth of the human renal carcinoma A498 in nude mice

Provided by J Gibbons, Wyeth Research.

***mTOR and HIF-α Activation and Inhibition***


***Novel Molecular Changes : RCC***

- Angiogenesis:
  - Integrins
  - Thrombospondin
  - Connexin32
- Hypoxia-inducible genes:
  - Epo/EpoR
  - CAIX
  - HIG2 (hypoxia inducible protein-2)
- Associated with aggressive phenotypes:
  - Smac/DIABLO
  - SPARC
  - Survivin
  - HIFα (decreased)
Summary

- Inhibitors of VEGF, VEGFR tyrosine kinases, and mTOR demonstrate anti-angiogenic and antitumor activity in renal cell carcinoma (RCC).
- Multiple molecular aberrations occur in RCC oncogenesis; identification and validation of new therapeutic targets remains a priority.
- Combination therapies that inhibit multiple molecular targets in oncogenic signaling and angiogenic pathways should further improve results in the clinic.
Novel Treatments for Advanced RCC
Jonathan Rosenberg, MD

Advanced renal-cell carcinoma (RCC) is highly resistant to chemo- and hormonal therapies, and previously has been primarily treated with cytokine-based therapy. Transient responses and limited long-term survival have been achieved in some patients. Side-effects are considerable, especially with high-dose interleukin (IL)-2. Clearly, there is an urgent need to pursue additional options for advanced stage RCC.

During the past decade, researchers have identified the von Hippel-Lindau (VHL) protein as an important tumor suppressor in clear-cell RCC. Elucidation of the VHL gene product (pVHL) and its regulation of hypoxia-inducible factor signaling have created a potential genetic basis for growth factor-targeted strategies in this disease. In the absence of normal VHL function, HIF accumulates and leads to abnormalities in glucose transport, autocrine growth stimulation, and angiogenesis (via overexpression of numerous angiogenic receptors, including VEGF and PDGF).

Insights into the molecular biology of RCC have revealed a key-role for vascular endothelial growth factor (VEGF) in the stimulation of angiogenesis in RCC, a highly vascularized tumor. Preclinical studies have shown that VEGF is involved in tumor growth and metastasis formation, and therefore, inhibition of tumor angiogenesis may be a promising therapeutic modality. This opens interesting new treatment strategies including: blocking VEGF with the monoclonal antibody bevacizumab and inhibition of multiple receptor tyrosine kinases (i.e., sunitinib or AG-013736). Likewise, inhibition of the Raf kinase pathway (i.e., sorafenib) or inhibition of the mTOR pathway (i.e., CCI-779, temsirolimus) are other options under investigation. The recent approval of two novel agents (sunitinib, sorafenib) confirms the hypothesis that receptor-mediated signaling (i.e., VEGF, PDGF) is an effective therapeutic target in RCC. This presentation will review recent data and present ongoing studies with novel therapies in advanced RCC.
Rosenberg - Novel Treatments for Advanced RCC

Novel Treatments for Advanced Renal Cell Carcinoma

Jonathan Rosenberg, MD
UCSF Cancer Center
San Francisco, CA

RCC: Current Therapeutic Options Are Inadequate

- RCC highly resistant to current chemotherapeutic agents
- Interferon-α
  - 15% objective response rate (ORR)
  - responses rarely complete or durable
  - modest survival benefit compared with placebo or ineffective therapies
- High-dose interleukin-2
  - 15-20% ORR in stage IV patients
  - only 5% complete responders
- No overall benefit to high dose IL-2 compared to low dose therapy
  - 3-5% of patients have durable responses
- Urgent need to pursue additional options for late-stage RCC treatment

Consequence of VHL Gene Mutation

- Elongin B/C
- Cul2
- Rbx1
- Ubiquitin Ligase Complex Disrupted
- HIF Accumulation
  - VEGF
  - Glut-1
  - TGF-α
- Angiogenesis
- Glucose Transport
- Autocrine Growth Stimulation
Bevacizumab in mRCC: Study Design

- Humanized monoclonal anti-VEGF antibody
- Binds and neutralizes all biologically active forms of VEGF

mRCC patients
N=116
ECOG PS <2
All patients have prior therapy (mostly IL-2)

Randomization

IV every 2 weeks

High dose = 10 mg/kg (n=39)
Low dose = 3 mg/kg (n=37)
Placebo (n=40)

Second randomization of placebo group at TTP to low-dose bevacizumab with or without thalidomide.

Bevacizumab Phase 2 Trial: Progression-Free Survival (PFS)

Patients Free of Tumor Progression (Percent)

High-dose Bevacizumab
Low-dose Bevacizumab
Placebo

High-dose Bevacizumab p < 0.001
Low-dose Bevacizumab p = 0.041

Change in Tumor Burden During Bevacizumab Therapy
Bevacizumab Plus Erlotinib in mRCC: Single-Arm Study

- N=63 patients with mRCC\(^1,2\)
- PFS rates at 1 year and 2 years were 45% and 24%, respectively.\(^2\)
  - Median TTP and median survival were 11.1 months and 22.8 months, respectively.

<table>
<thead>
<tr>
<th>Response (N=59)(^2)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>3</td>
</tr>
<tr>
<td>PR</td>
<td>22</td>
</tr>
<tr>
<td>SD/Minor response(^1)</td>
<td>61</td>
</tr>
<tr>
<td>PD</td>
<td>14</td>
</tr>
</tbody>
</table>

\(^1\)59/63 patients were included in the response analysis.
\(^2\)13 patients (22%) had minor responses.


Bevacizumab vs Bevacizumab Plus Erlotinib in mRCC: Randomized Phase 2 Study Design

- Primary end points: PFS and ORR

> “Preliminary estimates suggested that the addition of erlotinib to bevacizumab resulted in progression-free survival and response rates similar to those achieved with bevacizumab alone. …At this time we do not believe further studies of this particular combination in kidney cancer are warranted.”


Bevacizumab Plus IFN-α vs IFN-α in mRCC (CALGB): Phase 3 Study Design

- Primary objective: OS
- Preliminary results are expected in 2007

Rosenberg - Novel Treatments for Advanced RCC
Sunitinib (SU11248)

- Small-molecule receptor tyrosine kinase inhibitor
- Inhibits all VEGFRs, PDGFR-A, PDGFR-B, c-KIT, and FLT-3
- Oral administration
- Both antitumor and antiangiogenic activity
- FDA approved January 26, 2006 for treatment of advanced RCC

FGFR-1=fibroblast growth factor receptor; FLT-3=FMS-like kinase 3.

### Sunitinib Approval in Advanced RCC Based on*:

<table>
<thead>
<tr>
<th>RCC</th>
<th>Trial Type</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Single-arm, Phase 2 multi-center, open-label trials. Patients with MRCC who experienced failure of prior cytokine-based therapy.</td>
<td>Primary: Objective response rate (ORR, CR + PR) Secondary: Duration of response</td>
</tr>
<tr>
<td>(N=106)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=63)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Approval for advanced RCC is based on partial response rates and duration of responses. There are no randomized trials of sunitinib demonstrating clinical benefit such as increased survival or improvement in disease-related symptoms in RCC.
CR= complete response; ORR= objective response rate; PR= partial response.

### Sunitinib in mRCC: Phase 2 Study Design

Two independent, single-arm, multicenter, phase 2 trials (Trial 1: N=106; Trial 2: N=63)

- Primary end point: ORR
- Secondary end points: TTP, OS, safety

Motzer RJ et al. Paper presented at: ASCO; May 15-17, 2005; Orlando, FL.
Sunitinib Advanced RCC Trials
Study Design

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2 *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>Clear cell</td>
<td>Any RCC</td>
</tr>
<tr>
<td>Prior nephrectomy required for inclusion</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prior cytokine failure definition</td>
<td>Radiographic evidence of disease progression during or within 9 months of completion of 1 cytokine therapy treatment†</td>
<td>Disease progression or unacceptable treatment – related toxicity</td>
</tr>
</tbody>
</table>

*Assessed by investigators
† IFN α, IL-2, or IFNα plus IL-2; patients who were treated with IFNα alone must have received treatment for at least 28 days.


Sunitinib Advanced RCC Trials
Baseline Characteristics

- Comparable between Study 1 and Study 2: age, ECOG performance status

In Combined Population:
- ECOG performance status <2: 100%
- Median age: 57 years
- Component of clear-cell history: 95%
- Prior nephrectomy: 97%
- Received 1 previous cytokine regimen: 100%
- Most common site of metastases at baseline: lung: 81%
- ≥3 metastatic sites: 52%


Sunitinib Efficacy in Advanced RCC

<table>
<thead>
<tr>
<th></th>
<th>Study 1 (N=106)</th>
<th>Study 2 (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate (PR) (95% CI)</td>
<td>25.5%*(17.5, 34.9)</td>
<td>36.5%** (24.7, 49.6)</td>
</tr>
<tr>
<td>Duration of Response (95% CI)</td>
<td>27.1 weeks (24.4, 31) 6.2 months</td>
<td>54 weeks (34.3, 70.1) 12.5 months</td>
</tr>
</tbody>
</table>

*CI = confidence interval; PR = partial response.
** Assessed by blinded core radiology laboratory (central review)
† Data not mature enough to determine upper confidence limit
CI* = central 95% confidence interval; PR = partial response.
† Data not mature enough to determine upper confidence limit.
**Sunitinib in mRCC: Response Rates**

<table>
<thead>
<tr>
<th>Best response by RECIST</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>70 (41)</td>
</tr>
<tr>
<td>Stable disease (SD) ≥3 months</td>
<td>44 (26)</td>
</tr>
<tr>
<td>Progressive disease or SD &lt;3 months</td>
<td>45 (27)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>10 (6)</td>
</tr>
</tbody>
</table>

**Sunitinib in mRCC: Trial 1 Maximum Reduction of Target Lesions**

![Graph showing change from baseline (%)](image)

**Sunitinib in mRCC: Example of a Tumor Response**

![Images of tumor response](image)
Progression-Free Survival
Trials 1 and 2 Combined

Proportion of Patients Progression-Free

Sunitinib Therapy (Months)

Median PFS:
Trial 1: 8.7 months
Trial 2: 8.1 months
Combined: 8.2 months
(95% CI: 7.8, 10.4)


Sunitinib in mRCC: Overall Survival

Estimated survival probability (%)

Motzer RJ et al. Paper presented at: ASCO; May 13-17, 2005; Orlando, FL.

Sorafenib: Mechanism of Action

• Small-molecule receptor tyrosine kinase inhibitor
• Inhibits VEGFR-2, VEGFR-3, FLT-3, PDGFR, c-KIT, and Raf kinases
• Oral administration
• FDA approved December 20, 2005 for treatment of advanced RCC

**Sorafenib in mRCC: Randomized Phase 2 Discontinuation Trial Design**

- 12-week induction
- >25% shrinkage, continue sorafenib open label
- >25% to <25% randomized
- >25% growth, Off study

<table>
<thead>
<tr>
<th>Baseline</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Primary end points: PFS from day 1, PFS 12 weeks after randomization, tumor response rate, safety

*May cross over to Sorafenib.
Ratain MJ et al. Paper presented at: ASCO; May 13-17, 2005; Orlando, FL.

---

**Sorafenib in mRCC: Median Progression-Free Survival**

- Median Progression-Free Survival
- Sorafenib (n=33)
- Placebo (n=32)
- Censored

- Median PFS from randomization
  - Sorafenib = 24 weeks
  - Placebo = 6 weeks
  - P = 0.0087

- Proportion of patients progression-free
  - 100%
  - 75%
  - 50%
  - 25%

- Days from randomization
  - 0
  - 12-week run-in period

Ratain MJ et al. Paper presented at: ASCO; May 13-17, 2005; Orlando, FL.

---

**Sorafenib in mRCC: Phase 3 Study Design**

- Unresectable and/or metastatic RCC
- Clear-cell histology
- 1 prior systemic therapy in last 8 months
- N=909* ECOG PS 0/1

- Randomization
  - n=452 Placebo
  - n=451 A

- Primary end point: OS
- Secondary end points include response rates, PFS, safety, health-related quality of life

*Out of 905 patients randomized by February 15, 2005.
### Sorafenib in mRCC: Phase 3 Response Rate

<table>
<thead>
<tr>
<th>Best response by RECIST</th>
<th>Sorafenib (n=451)* (%)</th>
<th>Placebo (n=452)* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>43 (10)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>333 (74)</td>
<td>239 (55)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>56 (12)</td>
<td>167 (37)</td>
</tr>
<tr>
<td>Missing</td>
<td>18 (4)</td>
<td>38 (8)</td>
</tr>
</tbody>
</table>

*Patients randomized at least 6 weeks before data cut-off of May 31, 2005.


---

### Phase 3 Sorafenib in RCC: Maximum Percent Reduction in Tumor Measurement*

<table>
<thead>
<tr>
<th>Percentage Change from Baseline</th>
<th>Placebo</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>76%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Investigator assessed measurements


---

### Phase 3 Sorafenib in RCC: Tumor Response

- **21 June 2005**
- **Patient 251-050**
- **17 October 2005**

**Phase 3 Sorafenib in RCC: Progression-Free Survival Benefit**

- **Based on investigator assessment**

- **Proportion of Patients Progression-Free**

- **Time from Randomization (Months)**

- **Sorafenib**

- **Placebo**

- **Censored observation**

- **Median PFS**
  - Sorafenib = 5.5 months
  - Placebo = 2.8 months

- **Hazard ratio (S/P)** = 0.51


**Phase 3 Sorafenib in RCC: Planned Interim Analysis of Overall Survival**

- **Results are from a planned interim analysis as per protocol (220 events) and are considered preliminary**

- **Threshold for significance of interim analysis was p<0.0005**

- **Median OS**
  - Placebo = 14.7 months
  - Sorafenib = Not reached

- **Hazard ratio (S/P)** = 0.72

- **p-value** = 0.018**


**Phase 3 Sorafenib in RCC: Progression-Free Survival Across Patient Subgroups**

- **Sorafenib benefit**

- **Placebo benefit**

- **Age <65 years**

- **Age ≥65 years**

- **Low MSKCC score**

- **Intermediate MSKCC score**

- **No prior IL-2/Interferon**

- **Prior IL-2/Interferon**

- **No metastasis in lung at baseline**

- **Metastasis in lung at baseline**

- **No metastasis in liver at baseline**

- **Metastasis in liver at baseline**

- **Time from diagnosis <1.5 years**

- **Time from diagnosis ≥1.5 years**

- **Hazard ratio**

AG-013736

- Potent small molecule inhibitor of all known VEGFRs, PDGFR, and c-Kit
- Tested in a single-arm, multicenter trial
- Treatment
  - AG-013736 5 mg orally twice daily continuously until disease progression or unacceptable toxicity
  - Response assessed by RECIST criteria

Rini B, et al. ASCO 2005, abstract 4509

AG-013736 Phase 2 Trial: Best Response by RECIST (n=52)

- 46% Partial Response (n=24)
- 40% Stable Response (n=20)
- 14% Progression Indeterminate (n=7)
- 6% No Response (n=3)

Rini B, et al. ASCO 2005, abstract 4509

CCI-779 (Temsirolimus) Phase 2 Trial

- Novel mammalian target of rapamycin (mTOR) kinase inhibitor
- Exhibits immunosuppressive and anti-tumor activity
- Randomized phase 2 study of CCI-779:
  - 25 mg weekly infused over 30 minutes
  - 75 mg weekly infused over 30 minutes
  - 250 mg weekly infused over 30 minutes

CCI-779 Phase 2 Trial:
Tumor Response Rates*

<table>
<thead>
<tr>
<th>CCI-779 Dose Level</th>
<th>Total (n=111)</th>
<th>25 mg (n=36)</th>
<th>75 mg (n=38)</th>
<th>250 mg (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>20 (18.0%)</td>
<td>7 (19.4%)</td>
<td>5 (13.2%)</td>
<td>8 (21.6%)</td>
</tr>
<tr>
<td>PR</td>
<td>7 (6.4%)</td>
<td>3 (8.3%)</td>
<td>6 (15.8%)</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>CR/PR</td>
<td>27 (24.3%)</td>
<td>10 (27.8%)</td>
<td>11 (28.9%)</td>
<td>6 (16.2%)</td>
</tr>
<tr>
<td>SD ≥ 8 weeks &lt; 24 weeks</td>
<td>49 (44.3%)</td>
<td>18 (50.0%)</td>
<td>17 (44.7%)</td>
<td>14 (37.8%)</td>
</tr>
<tr>
<td>SD ≥ 24 weeks</td>
<td>29 (26.2%)</td>
<td>5 (13.9%)</td>
<td>8 (21.0%)</td>
<td>6 (16.2%)</td>
</tr>
<tr>
<td>CR/PR/MR/SD ≥ 24 weeks</td>
<td>6 (5.4%)</td>
<td>2 (5.6%)</td>
<td>3 (8.0%)</td>
<td>1 (2.7%)</td>
</tr>
</tbody>
</table>


CCI-779 Phase 2 Trial:
Time-to-Progression

<table>
<thead>
<tr>
<th>CCI-779 mg</th>
<th>n</th>
<th>Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>35</td>
<td>6.3</td>
<td>3.7, 7.2</td>
</tr>
<tr>
<td>75</td>
<td>38</td>
<td>6.7</td>
<td>3.5, 8.3</td>
</tr>
<tr>
<td>250</td>
<td>37</td>
<td>5.2</td>
<td>3.7, 7.4</td>
</tr>
</tbody>
</table>

Log-Rank Test: \( p = 0.933 \)

CCI-779 in Advanced RCC:
Randomized Phase 3 Trial Design*

<table>
<thead>
<tr>
<th>Advanced RCC First-line high-risk patients N=600 (200 per arm) Sites ~165 Mostly clear-cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-α escalating as tolerated to 18M IU SC TIW</td>
</tr>
<tr>
<td>CCI-779 25 mg IV q Wk</td>
</tr>
<tr>
<td>CCI-779 15 mg IV q Wk + IFN-α 6M IU SC TIW</td>
</tr>
</tbody>
</table>

*Primary end point: Survival

*(Stage 4 or recurrent disease. Available at: http://www.clinicaltrial.gov/ct/show/NCT00065468?order=1)

Rosenberg - Novel Treatments for Advanced RCC
Summary and Conclusions

- Bevacizumab inhibits tumor angiogenesis and shows activity in mRCC.
- In a phase 3 placebo-controlled trial, sorafenib significantly prolongs PFS (167 days) compared with placebo (84 days) in patients with advanced RCC.
- In a phase 2 setting, sunitinib induces objective responses in 40% of patients with cytokine-refractory RCC.
- The multi-kinase inhibitor AG-013736 and mTOR inhibitor CCI-779 demonstrate activity in phase 2 trials in patients with advanced RCC.
- Combination trials of molecular targeted agents and cytokines are ongoing in both the adjuvant and metastatic setting.
- The optimal regimen in mRCC using these agents has yet to be defined.

Summary of Phase 2/3 RCC Trials

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Sponsor</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3 sorafenib vs placebo</td>
<td>Bayer/Oncyx</td>
<td>Completed</td>
</tr>
<tr>
<td>Phase 2 sorafenib vs interferon (IFN)</td>
<td>Bayer/Oncyx</td>
<td>Accruing</td>
</tr>
<tr>
<td>Phase 3 sunitinib vs IFN</td>
<td>Pfizer</td>
<td>Completed</td>
</tr>
<tr>
<td>Phase 3 bevacizumab + IFN vs IFN</td>
<td>Genentech</td>
<td>Completed</td>
</tr>
<tr>
<td>Phase 3 CCI-779 + IFN vs IFN</td>
<td>Wyeth</td>
<td>Completed</td>
</tr>
<tr>
<td>Phase 2 bevacizumab +/- sorafenib</td>
<td>Genentech</td>
<td>Completed</td>
</tr>
<tr>
<td>Bevacizumab + HD IL-2</td>
<td>Chiron/Genentech</td>
<td>Accruing</td>
</tr>
<tr>
<td>Bevacizumab + LD IL-2</td>
<td>Genentech</td>
<td>Accruing</td>
</tr>
<tr>
<td>Bevacizumab + sorafenib</td>
<td>CTEP</td>
<td>Accruing</td>
</tr>
<tr>
<td>Bevacizumab + sunitinib</td>
<td>Pfizer</td>
<td>Accruing</td>
</tr>
<tr>
<td>Neo-adjuvant sunitinib</td>
<td>CTEP</td>
<td>Accruing</td>
</tr>
<tr>
<td>Sunitinib in bevacizumab-refractory pts</td>
<td>Pfizer</td>
<td>Completed</td>
</tr>
<tr>
<td>AG-013736 in sorafenib-refractory pts</td>
<td>Pfizer</td>
<td>Accruing</td>
</tr>
<tr>
<td>Adjuvant sunitinib, sorafenib, or placebo</td>
<td>ECOG</td>
<td>In Development</td>
</tr>
</tbody>
</table>
Renal cell carcinoma (RCC) arises from the renal epithelium and account for about 90% of kidney cancers. Prognosis is closely related to the stage and grade of the disease at diagnosis. Nephrectomy is the primary treatment for localized RCC. However, up to a third of the patients undergoing resection for localized disease will experience recurrence. Median survival for patients with metastatic disease is about 13 months.

In patients who are expected to have greater than 50% probability of recurrence after nephrectomy, adjuvant therapy would be desirable. Attributes of an ideal adjuvant therapy include demonstrated efficacy in metastatic setting, convenient outpatient administration, and low toxicity. Various adjuvant therapies have been evaluated in Phase III clinical trials, and thus far, only a German study with autologous tumor vaccine has demonstrated benefit.

This presentation will review the various adjuvant therapy trial results as well as ongoing and future planned adjuvant trials. Current approaches using molecular targeted therapies before cytoreductive nephrectomy to gain insight into the biology of RCC and effect of novel agents will also be reviewed.
Adjuvant and Pre-Surgical Therapy for RCC

Nizar Tannir, MD, FACP
The Department of Genitourinary Medical Oncology

TNM of RCC

<table>
<thead>
<tr>
<th>Tumor (T)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor 7cm or less confined to the kidney</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 7cm confined to the kidney</td>
</tr>
<tr>
<td>T3a</td>
<td>Tumor invades adrenal gland or perinephric tissues, but not beyond Gerota’s fascia</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor grossly extends into renal vein or IVC</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor beyond Gerota’s fascia</td>
</tr>
</tbody>
</table>

TNM of RCC

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>LN cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional LN mets</td>
</tr>
<tr>
<td>N1</td>
<td>Mets in a single lymph node 2 cm or less</td>
</tr>
<tr>
<td>N2</td>
<td>Mets in a single LN &gt;2 cm, but not &gt;5 cm, or multiple LNs none &gt;5 cm</td>
</tr>
<tr>
<td>N3</td>
<td>Mets in a lymph node &gt;5 cm</td>
</tr>
</tbody>
</table>
TNM of RCC

<table>
<thead>
<tr>
<th>Distant Metastasis (M)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant mets cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant mets</td>
</tr>
<tr>
<td>M1</td>
<td>Distant mets</td>
</tr>
</tbody>
</table>

Risk Factors for Relapse After Nephrectomy

- T2 Fuhrman nuclear grade 3, 4
- T3, T4
- Any N

Attributes of the Ideal Adjuvant Drug

- Effective in the metastatic setting
- Convenience of outpatient administration
- Low toxicity profile
Randomized Phase III Trials

<table>
<thead>
<tr>
<th>Intervention</th>
<th>N</th>
<th>Group</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>72</td>
<td>Scandinavian</td>
<td>No</td>
</tr>
<tr>
<td>MPA</td>
<td>136</td>
<td>Italian</td>
<td>No</td>
</tr>
<tr>
<td>Autologous tumor cells + BCG</td>
<td>120</td>
<td>Italian</td>
<td>No</td>
</tr>
<tr>
<td>IFN</td>
<td>247</td>
<td>Italian</td>
<td>No</td>
</tr>
<tr>
<td>IFN</td>
<td>283</td>
<td>US Intergroup</td>
<td>No</td>
</tr>
<tr>
<td>HD IL-2</td>
<td>69</td>
<td>CWG</td>
<td>No</td>
</tr>
<tr>
<td>HSPPC '96 (Oncophage®)</td>
<td>818</td>
<td>Antigenics</td>
<td>No</td>
</tr>
<tr>
<td>Autologous tumor vaccine</td>
<td>558</td>
<td>German</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Current and Future Trials

- cG250 monoclonal antibody vs placebo
- SCORE trial (sorafenib vs placebo)
- ECOG trial (sorafenib vs sunitinib vs placebo)

SCORE Trial

RANDOMIZATION

Placebo 3 years
Sorafenib 1 year Placebo 2 years
Sorafenib 3 years
**ECOG Trial**

**RANDOMIZATION**

- Placebo 1 year
- Sorafenib 1 year
- Sunitinib 1 year

**MDACC Bevacizumab-Erlotinib Trial**

Metastatic disease, no prior nephrectomy or therapy

- Bevacizumab 10mg/kg IV Q14 days
- Erlotinib 150mg PO QD For 8 weeks

- Response Or Stable
  - Nephrectomy, Continue Same Agents
- Progressive, Good PS
  - Nephrectomy, New Chemo
- Progressive, Poor PS
  - New Chemo, Or Best Supportive Care

Companion dynamic contrast imaging study

**MDACC Sorafenib Presurgical Trial**

Metastatic disease, no prior nephrectomy or therapy

- Nephrectomy, Then 10 wks Sorafenib
- Stable/Respond
  - Continue Sorafenib
- 1 wk Sorafenib, Nephrectomy, Then 9 wks Sorafenib
- Progression
  - New Chemo
- 4 wks Sorafenib, Nephrectomy, Then 6 wks Sorafenib
Reading List


