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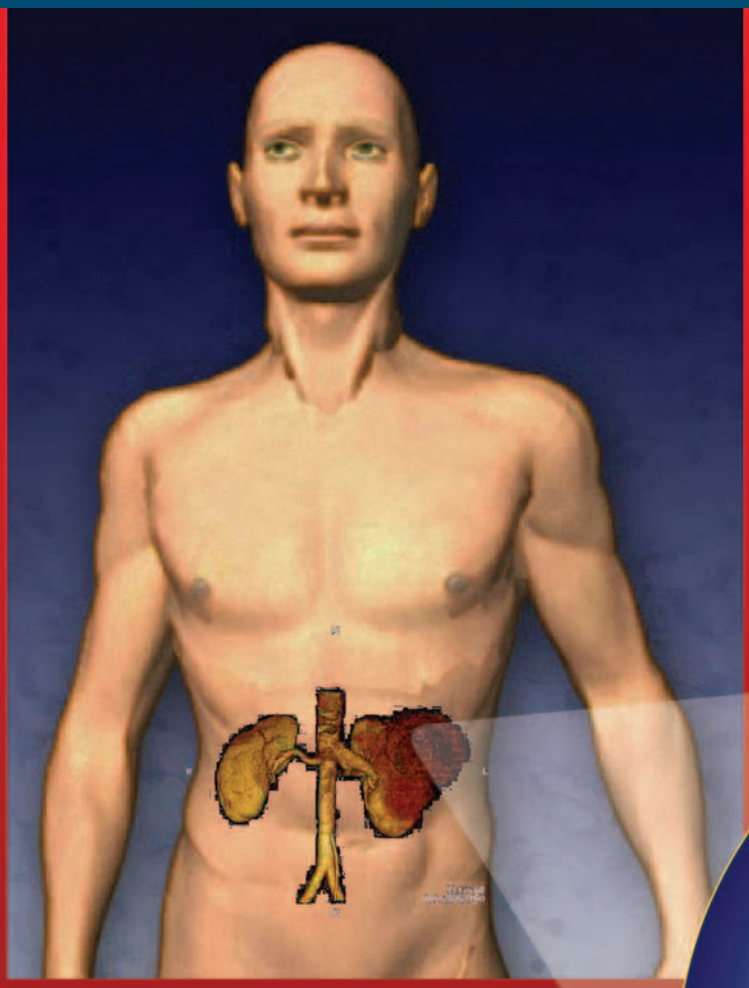

Blockade of Molecular Chaperone, B7-H1, Could Improve Immunotherapy in RCC

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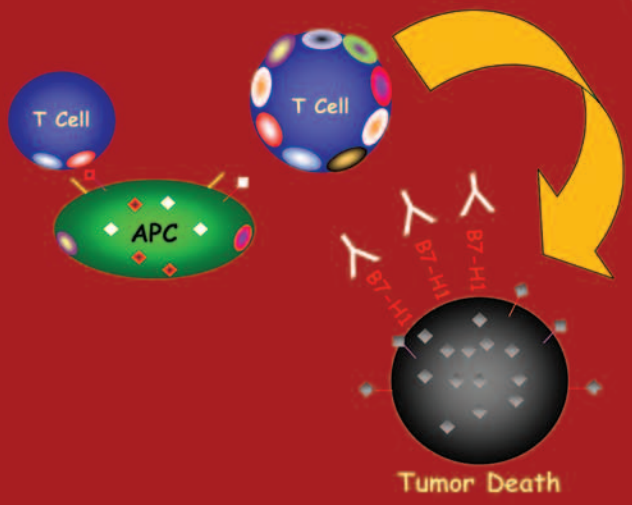

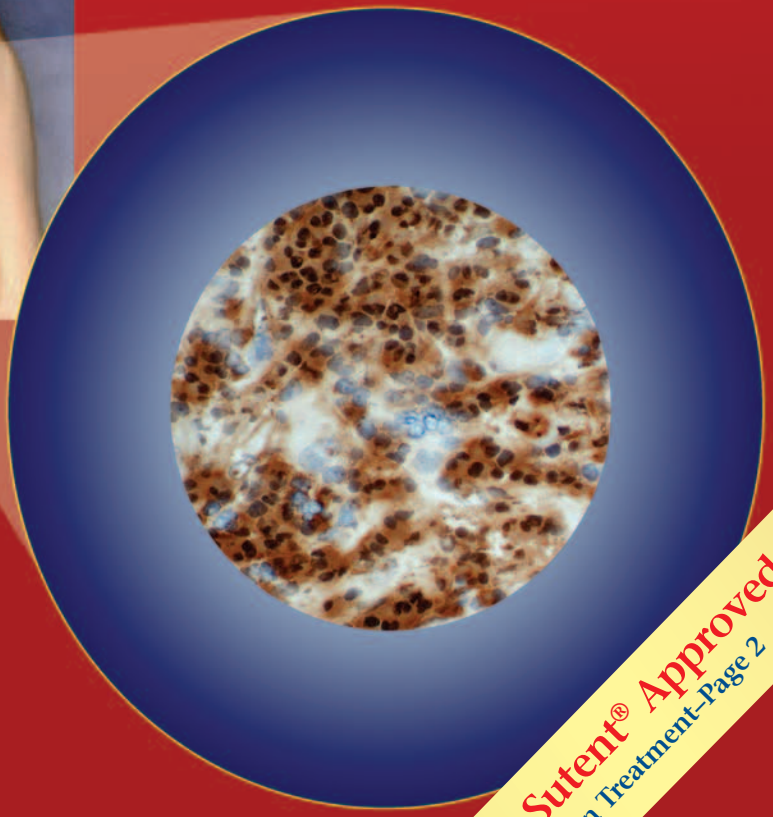

Nexavar®, Sutent® Approved
A Milestone in Treatment–Page 2

An Educational Service for Medical Oncologists and Urologists

Editorial Mission
The purpose of *Kidney Cancer Journal* is to serve as a comprehensive resource of information for physicians regarding advances in the diagnosis and treatment of renal cell carcinoma. Content of the journal focuses on the impact of translational research in oncology and urology and also provides a forum for cancer patient advocacy. *Kidney Cancer Journal* is circulated to medical oncologists and urologists.

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About the Cover
Illustration depicts mechanisms operating on the surface of tumor cells and T cells that could result in death of tumor cell if a pivotal molecule, B7-H1, can be neutralized. The presence of B7-H1 on tumor cell suggests a poor prognosis but if activity of T cells can be enhanced, effect of B7-H1 can be blocked. On the right, magnification shows renal cell carcinoma specimen with high tumor-associated B7-H1 expression. (Images courtesy of Eugene D. Kwon, MD, and R. Houston Thompson, MD)

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KCJ EDITOR'S MEMO

Robert A. Figlin, MD

Nexavar®, Sutent® Drive Home the Message: Bench to Bedside Research in Kidney Cancer Is the Only Path to Finding a Cure

As clinicians involved with the treatment of advanced kidney cancer, we all look forward to a new era in treatment with the recent announcement of FDA approval of Nexavar (sorafenib), and Sutent (sunitinib), the first such approvals for this indication in more than 10 years. The approval of Nexavar and Sutent reflects the culmination of years of hard work by dedicated investigators worldwide engaged in the study of their use in more than 4,000 patients to date.

Specifically in renal cell carcinoma, the road to approval of Nexavar is detailed in the timeline shown on page 3. Data supporting use of the agent grew over the years and the excitement surrounding its mechanism of action alerted us, as investigators, to a new era in other respects as well—the importance of identifying pathways of disease and novel molecular chaperones—thus paving the way for use of targeted therapies.

It is this excitement—the identification of new downstream targets and the potential for additional molecules to come to market—that will hold our focus in the coming years as we expect to see other drugs blocking tumor growth in innovative ways. Nexavar, for example, has been shown to target members of multiple classes of kinases known to be involved in both tumor cell proliferation and tumor angiogenesis. These kinases include RAF kinase, VEGFR-2, VEGFR-3, PDGFR-B, KIT, and FLT-3. In this sense, it is the first oral multikinase inhibitor that targets receptor kinases in both the tumor cell and the tumor vasculature. Which of these kinases Nexavar preferentially attacks awaits further research, although the leading candidate kinases are VEGFR-2 and PDGFR-B.

As much as we are encouraged by the approval of new agents such as Nexavar and Sutent, our attention gravitates toward the use of these classes of agents in the adjuvant setting and the identification of new targets such as B7-H1, a cell-surface glycoprotein that is the subject of one of our articles in

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For information on regional CME programs on kidney cancer please respond to the business reply card on page 10.

Tracking Trends from Web-based Sources, Industry, and Translational Research

FDA Approves Sutent® for Advanced Kidney Cancer

WASHINGTON—The Food and Drug Administration (FDA) has approved Sutent (sunitinib), a new targeted anti-cancer treatment for patients with gastrointestinal stromal tumors (GIST) and advanced kidney cancer. The FDA action marks the first time the agency has approved a new oncology product for two indications simultaneously. Sutent, which received a priority review and was approved in less than 6 months, is a tyrosine kinase inhibitor working through multiple targets. "Today's approval is a major step forward in making breakthrough treatments available for patients with rare and difficult to treat forms of cancer," said Steven Galson, MD, Director of FDA's Center for Drug Evaluation and Research. "New targeted therapies such as Sutent are helping FDA expand options for patients for whom there are limited alternatives."

According to the American Cancer Society, about 32,000 new cases of advanced kidney cancer and 5,000 cases of GIST are diagnosed each year. In contrast to the approval for GIST, which was based on the drug's ability to delay the growth of the tumors, the approval for renal cell carcinoma was based on Sutent's ability to reduce the size of the tumors in patients. An overall response rate ranging from 26-37 percent was found in patients with metastatic kidney cancer whose tumors had progressed following cytokine-based therapy." Approval of this drug for these indications provides compelling evidence that the use of alternative data endpoints allows us to see the benefits of novel therapies earlier in patients," said Richard Pazdur, MD, Director of FDA's Office of Oncology Drug Products.

For the RCC indication, the FDA used its accelerated approval process, a regulatory mechanism that expedites drug approvals for serious and life-threatening diseases. FDA worked with Pfizer Oncology to offer an expanded access program prior to approval, making the product available to patients not enrolled in a clinical trial. Currently, more than 1700 patients are being treated with Sutent through the expanded access program.

In the latest study, published in the January 2006 issue of the *Journal of Clinical Oncology*, Motzer et al demonstrated the drug's antitumor activity in metastatic RCC as second-line therapy. Sunitinib is a small molecule inhibitor with high binding affinity for VEGF and PDGF receptors. In a multicenter phase 2 trial of patients with metastatic RCC and progression on first-line cytokine therapy, sunitinib was administered in repeated responses; 17 additional patients (27%) demonstrated stable disease lasting > or = 3 months. Median time to progression in the 63 patients was 8.7 months.

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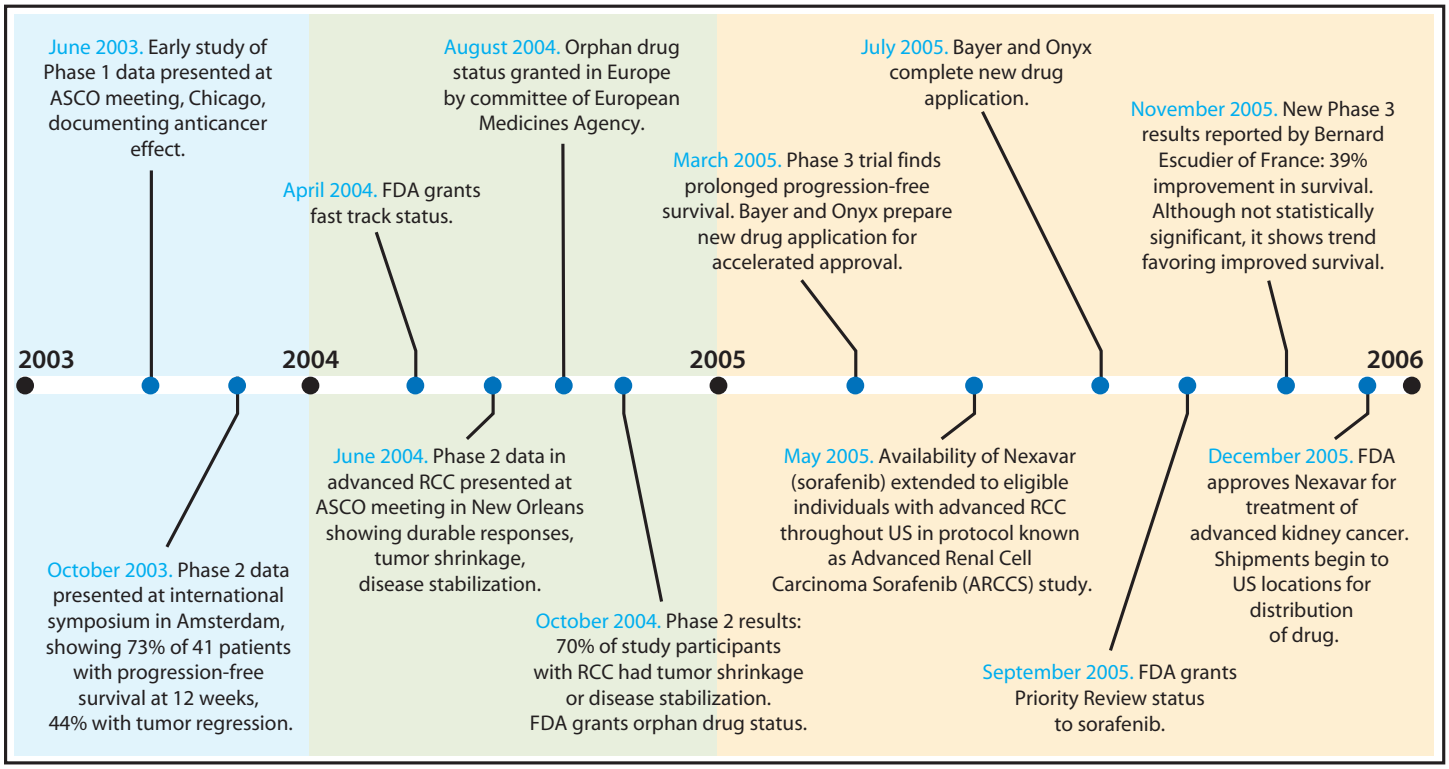
Nexavar's Fast Track to FDA Approval

How a new molecule emerged as the first new kidney cancer treatment in more than 10 years



Editor's note: Patients concerned about issues related to insurance co-payment assistance should the contact the Patient Advocate Foundation at www.patientadvocate.org. The Kidney Cancer Asssociation (KCA) will be working with this group. Patient queries about the drug itself can be addressed to the KCA Nurse Hotline: (800) 866-400-5151. The KCA Nurse Advisory Board is assisting in this effort.

Critical Reading: Current Selections from the Peer-Reviewed Literature

New data support study of mTOR inhibitors

Thomas GY, Tran C, Mellinghoff IK, et al. Hypoxia-inducible factor determines sensitivity to inhibitors of mTOR in kidney cancer. *Nat Med*. 2006;12:122-127.

Summary: Inhibitors of the kinase mammalian target of rapamycin (mTOR) have shown sporadic activity in cancer trials, leading to confusion about the appropriate clinical setting for their use. This study shows that loss of the von Hippel-Lindau tumor suppressor gene (VHL) sensitizes kidney cancer cells to the mTOR inhibitor CCI-779 in vitro and in mouse models. Growth arrest caused by CCI-779 correlates with a block in translation of mRNA encoding hypoxia-inducible factor (HIF1A), and is rescued by expression of a VHL-resistant HIF1A cDNA lacking the 5′ untranslated region. VHL-deficient tumors show increased uptake of the positron emission tomography (PET) tracer fluorodeoxyglucose (FDG) in an mTOR-dependent manner.

Conclusion: These findings provide preclinical rationale for prospective, biomarker-driven clinical studies of mTOR inhibitors in kidney cancer and suggest that FDG-PET scans may have use as a pharmacodynamic marker in this setting.

WX-G250 plus low-dose IL-2 shows clinical benefit

Bleumer I, Oosterwijk E, Oosterwijk JC, et al. A clinical trial with chimeric monoclonal antibody WX-G250 and low dose interleukin-2 pulsing scheme for advanced renal cell carcinoma. *J Urol*. 2006;175:57-62.

Summary: WX-G250 is a chimeric monoclonal antibody that binds to carbonic anhydrase $IX^{G250/MN}$, which is present on greater than 95% of renal cell carcinomas of the clear cell subtype. The suggested working mechanism of WX-G250 is by antibody-dependent cellular cytotoxicity (ADCC). Because the number of activated ADCC effector cells can be increased by a low-dose interleukin-2 pulsing schedule, a multicenter study was initiated to investigate whether WX-G250 combined with low-dose interleukin-2 could lead to an improved clinical outcome in patients with progressive renal cell carcinoma. A total of 35 patients with progressive clear cell disease received weekly infusions of WX-G250 for 11 weeks combined with a daily low-dose interleukin-2 regimen. Patients were monitored longitudinally for ADCC capacity. Radiological assessment of metastatic lesions was performed at week 16 and regularly until disease progres-

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GUEST EDITORIAL

Divided We Fall: How Competition Can Compromise the Cause

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William P. Bro
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Recent advancements in the treatment of kidney cancer have brought hope to thousands of patients diagnosed with the disease and their loved ones. But there is still much work to be done, and now more than ever, it is imperative that advocates remain united in their efforts to promote further research to fight this deadly disease. Unfortunately, recent factions in the kidney cancer advocacy community have challenged this unity and threaten to thwart this encouraging progress.

Patients are the first casualty when advocacy groups begin "competing" to serve a relatively small disease population such as kidney cancer. When someone is diagnosed with a serious disease, one of the first places he or she turns to for information and support is voluntary health organizations. However, when multiple organizations purport to represent patients' best interests, or worse, when they appear at odds over their approach to advocacy, it only serves to confuse patients. Paula Bowen, board chair of the Kidney Cancer Association (KCA), suggests greater cooperation would serve everyone's interests: "Kidney cancer advocacy organizations should consider development of working relationships with other domestic kidney cancer-specific charities. A unified approach is more effective than diverse cancer-specific groups promoting disparate agendas. We all want the same outcome."

Unity is perhaps even more important when it comes to research advocacy. The US Congress provides approximately $27 billion for medical research every year through the National Institutes of Health (NIH),[1] but

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Novel Molecular Chaperone, B7-H1, Promising Downstream Target to Improve Kidney Cancer Immunotherapy

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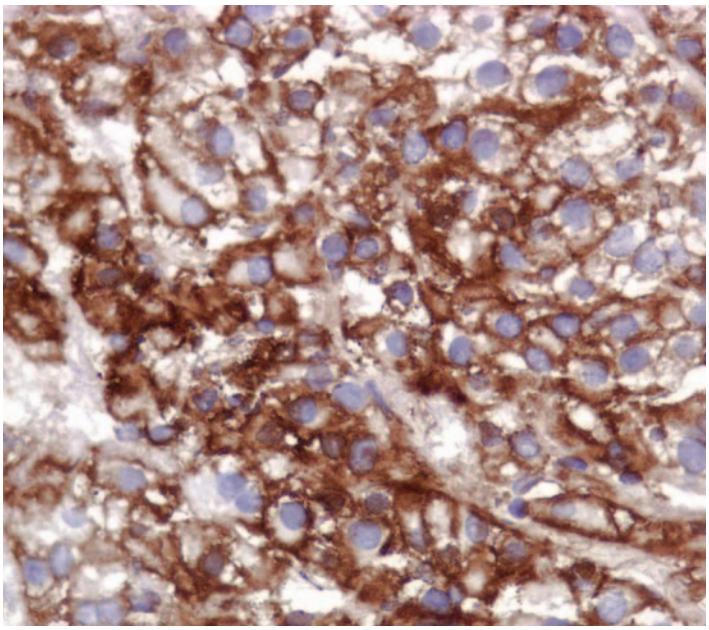
New knowledge about the immune receptor B7-H1 could work in several therapeutic ways: (1) To develop a drug to block B7-H1 to improve effectiveness of immunotherapy. Animal models show that B7-H1 can be used as a therapeutic target for an antibody that would bind it up and block its function. This may improve treatment responses for patients with kidney cancer by protecting their immune systems from being shut down. (2) To serve as a biomarker to determine prognosis. High levels of B7-H1 in a tumor biopsy would indicate a poor prognosis, and low levels or absence would suggest a good prognosis. (3) To help physicians plan therapy. Patients with low levels of B7-H1 may be the best candidates for immunotherapeutic treatment using agents such as interleukin-2 and alpha interferon.

A critical factor in tailoring new therapies for renal cell carcinoma is the need to discover pathways and mechanisms responsible for tumor progression and metastases. With the growing identification of molecular chaperones and a range of downstream targets, new therapies are emerging and targeting the mechanisms involved in the pathogenesis of kidney cancer. One of the most promising avenues of study is a costimulatory or coregulatory molecule expected to play a major role in efforts to augment current immunotherapy, including the treatment for metastases after cytoreductive nephrectomy.

This molecule is B7-H1, discovered by Dong et al in 1999.[1] A cell surface glycoprotein belonging to the B7 family of costimulatory molecules, it is believed to play a role in mediating T-cell immunity. Costimulatory molecules deliver positive and negative signals to modulate the threshold of T-cell activation.[2] Evidence is building for a strong connection between B7-H1 and a number of solid human malignancies,[3-5] supporting the view that the molecule functions as a negative regulator of T-cell-mediated immunity and operates in the periphery to inhibit antitumoral immune responses.

From previous reports, this much is known about B7-H1:

- Tumor cell expression of B7-H1 has been shown to enhance apoptosis of activated tumor-specific T cells in vitro[3]
- Induced B7-H1 expression on activated T cells impairs both T-cell function and survival,[6] and expression of B7-H1 on myeloid dendritic cells associated with ovarian carcinoma has been found to suppress T-cell activation[7]
- In murine cancer models, monoclonal antibody blockade of B7-H1 potentiates antitumoral responses
- B7-H1 may enhance immunosuppression in some tumors and may be a promising therapeutic target



Primary clear cell renal cell carcinoma specimen with high tumor B7-H1 expression. Magnification x400.

Cytokine-based immunotherapy, including the use of high-dose interleukin-2, has been shown to be effective in 15% of patients with renal cell carcinoma, implicating the disease as an immunogenic form of cancer amenable to immune-based therapy. However, the limited efficacy of this therapy, along with the toxicity of interleukin-2, has led investigators to redefine the criteria for subsets of patients who might benefit from cytokine therapy. Recent reports have gone a long way toward improving the criteria for patient selection, yet the potential mechanism whereby renal cell carcinoma impairs host immunity and facilitates subsequent tumor progression is still poorly understood.[2]

This is one of the reasons why evidence on B7-H1 is becoming ever more important as strategies are refined to optimize the efficacy of cytokine-based immunotherapy.

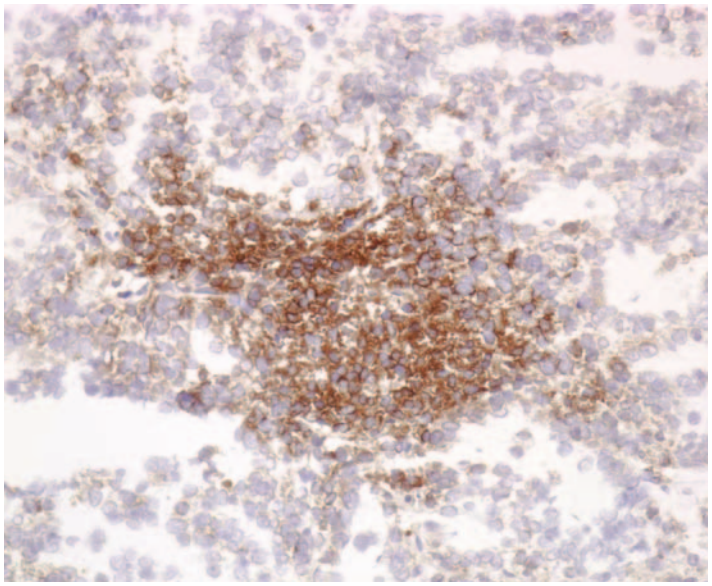
We know that the aberrant expression of B7-H1 translates into adverse pathologic features and a diminished cancer-specific survival in patients with renal cell carcinoma.[8] The latest findings take this association a step further by demonstrating—through additional follow-up—that patients harboring high B7-H1 levels are indeed at significantly increased risk of death even after multivariate adjustment.[2] The other story evolving with B7-H1 is its potential association in metastatic renal cell carcinoma. This association previously was unclear but data from our recent study have shown that B7-H1 expressed in metastatic disease deposits may play a pivotal role in facilitating tumor progression by impairing immune recognition.[2] This raises the possibility, although not yet sufficiently explored, that metastatic renal cell carcinoma also may be amenable to anti-B7-H1 immunotherapy.

Results from the Mayo Clinic in Primary and Metastatic Renal Cell Carcinoma

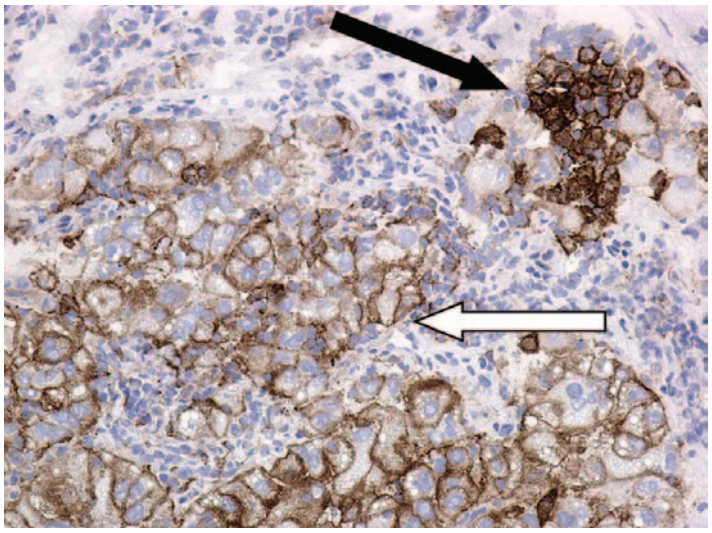
Compelling data from a 4-year study of 196 patients who underwent nephrectomy and 26 patients who had resection of renal cell carcinoma metastases for the clear cell subtype underscores the potential role of B7-H1 in both primary and metastatic tumors.[2] Variable levels of B7-H1 were expressed on primary tumor cells (n = 130; 66.3%) and primary tumor-infiltrating lymphocytes (n = 115; 58.7%). Patients with high expression of B7-H1 on primary tumor cells and/or lymphocytes were significantly more likely to die of renal cell carcinoma compared with patients with low B7-H1 expression (risk ratio = 4.17); $P \leq .001$). This risk remained after adjusting for the Mayo Clinic stage, size, grade, and necrosis score. The trend carried over into the metastatic setting: of 26 metastatic specimens, cancer cell and lymphocyte B7-H1 expression was demonstrated in 65.4% and 69.2%, respectively. Overall, 54.3% of metastatic specimens had high aggregate B7-H1 levels compared with 44.4% in primary specimens.

We believe the implications of these results are far reaching and will set a new direction for future renal cell carcinoma research. Until recently, relatively little has been known about B7-H1. In humans, cell surface B7-H1 expression is normally restricted to a fraction of macrophage-lineage cells and is not present in the normal human kidney.[3] By binding to the T-cell PD-1 (or a putative non-PD-1) receptor, tumor-associated B7-H1 can inhibit tumor-specific T-cell mediated immunity. In turn, B7-H1 thus induces T-cell apoptosis, impairs cytokine production, and diminishes the cytotoxicity of activated T cells.[3,9-11]

The role of B7-H1 has also been elucidated in activated T cells since they also express this molecule. Thus, B7-H1 serves to downregulate primed T-cell responses by similarly inducing apoptosis or inhibiting T-cell clonal expansion.[6] In a mouse model the advantages of blocking tumor-associated B7-H1 have been shown. Such blockade can potentiate antitumoral T-cell responses directed against both artificially transfected and endogenously expressed B7-H1 positive tumors.[15] Since B7-H1 impairs the function and survival of activated tumor-specific T cells, it may be pivotal in promoting tumor progression when the host's immune system is thereby compromised.



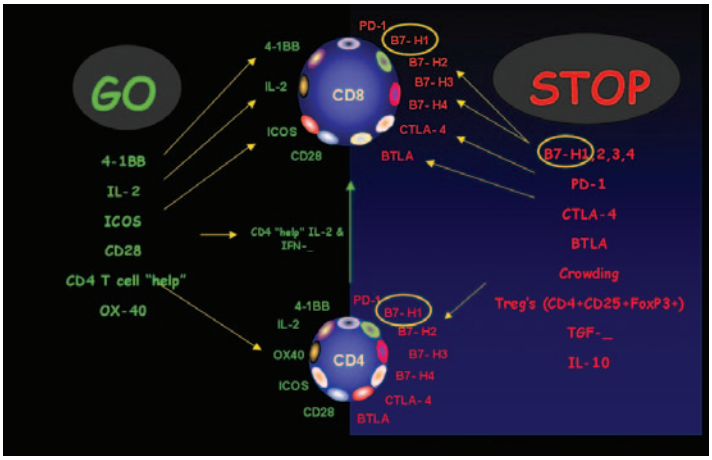
Primary clear cell renal cell carcinoma specimen with high lymphocyte B7-H1 expression. Magnification x200.



Metastatic clear cell renal cell carcinoma specimen to lung with high B7-H1 on both tumor cells (white arrow) and infiltrating lymphocytes (black arrow). Magnification x400.

Emerging concepts: regulating T-cell responses and their implications

To demonstrate the role of B7-H1, investigators have developed animal models to confirm its potential effect on T cells, antigen-presenting cells, and host tissue to inhibit effector T cell responses. B7-H1, also referred to in the literature as PD-L1, was studied in a mouse model by Latchman et al.[12] The authors generated B7-H1-deficient (B7-H1-/-) mice. The expression of B7-H1 within nonlymphoid tissue suggests that it may regulate self-reactive T or B cells in peripheral tissues and/or may regulate inflammatory responses in target organs, according to Latchman et al. Their recent study



In this schematic a broad range of factors and interactions are identified, all occurring at the cellular level, to influence T-cell-mediated responses. The T cells at the center of the diagram are CD8 and CD4. Positive factors are those shown at the left. Overall, these interactions, including those affecting various receptors, can ultimately determine the extent to which an immune response is either enhanced or inhibited. This response will determine whether cancer cells proliferate or undergo apoptosis.

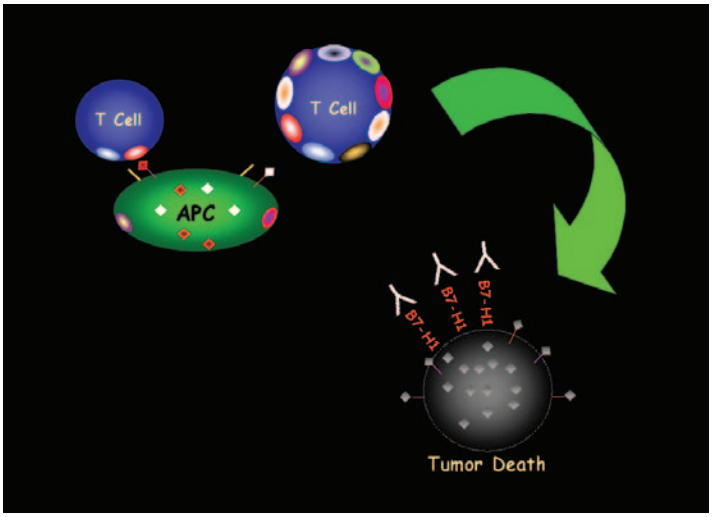
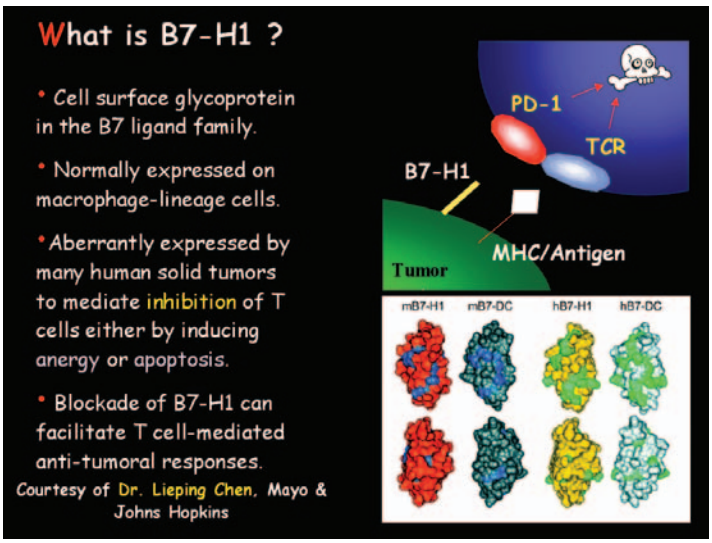
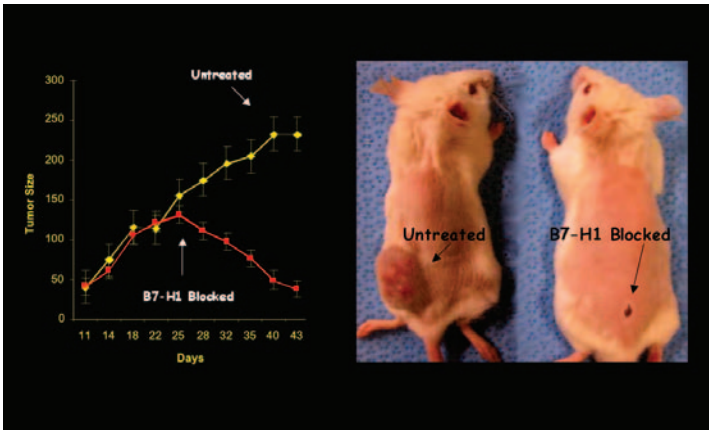


Illustration depicts mechanisms operating on the surface of tumor cells and T cells that could result in death of tumor cell if a pivotal molecule, B7-H1, can be neutralized. The presence of B7-H1 on tumor cell suggests a poor prognosis but if activity of T cells can be enhanced, effect of B7-H1 can be blocked.





Blockade of B7-H1 on tumor cells in mice enhances T-cell activity. The effect of such blockade, improving the effect of immunotherapy, is evident in this image suggesting regression of tumors in a mouse model.

sheds light on the importance of B7-H1 expression on T cells, antigen-presenting cells, and host tissues.

In the B7-H1-deficient mice, CD4+ and CD8+ T-cell responses were markedly enhanced compared with wild-type mice. Similarly, in the B7-H1-deficient mice, dendritic cells stimulated greater wild-type CD4+ T-cell responses than wild-type dendritic cells and these cells also produced more cytokine than wild-type CD4+ T cells. Other findings in this study pointed toward the importance of cell surface expression of B7-H1. For example, the mouse model explored the effect of inducing experimental autoimmune encephalomyelitis (EAE) in these mice. When B7-H1-/- T cells were adoptively transferred to B7-H1-/- recipients, a rapid onset of severe EAE occurred. Thus, it can be inferred that tumor cells that express B7-H1 grow in wild-type mice but are suppressed in PD-1-/- mice.[9] The implications from these findings are:

- B7-H1:PD-1-mediated inhibitory signals give tumors a selective advantage for growth by inhibiting CD8+ T-cell responses
- The enhanced CD8+ T-cell responses in B7-H1-/- mice, together with B7-H1 expression on tumors, suggest that B7-H1 on tumors may limit CD8+ T-cell clonal expression and thereby attenuate tumor-specific responses
- Blockade of the B7-H1/PD-1 pathway may provide a means to boost antitumor and antiviral immunity

Numerous additional studies are also building further evidence for the importance of B7-H1 and its role in contributing to immune evasion by cancers. Previous observations[1,3,13] delineate a cascade of events in which B7-H1 serves as a mediator functioning to inhibit T-cell responses. In one of these reports,[14] they note that upon ligation to its receptors on T cells, B7-H1 regulates activation and differen-

tiation of T cells. Although there are numerous potential mechanisms that could contribute to the resistance of solid tumors to immune effector mechanisms, a major consideration is the engagement of negative regulatory receptors on activated T cells by ligands expressed in the tumor microenvironment.[11]

According to Dong and Chen,[14] B7-H1 preferentially costimulates interleukin-10 production in resting T cells and further induces the apoptosis of activated T cells. Further, PD-1 is a receptor of B7-H1 and is shown to mediate the inhibition of activated T-cell response, presumably by inhibiting cell cycle progression. Unlike the expression of B7-H1 protein, limited to macrophage lineage of cells in normal tissues, B7-H1 is found abundantly in various human cancers. Tumor-associated B7-H1 increases apoptosis of antigen-specific T cells, leading to growth of immunogenic tumor in vivo.

Blockade of B7-H1 by monoclonal antibodies

The potential utility of blocking B7-H1 in the clinical setting is still a concept in search of confirmation in human trials, but the rationale for doing so is already supported by investigations such as those by Hirano et al[15] and Brown et al.[5] Aside from possibly explaining the limited success of T-cell-based immunotherapies, they predict that blockade of B7-H1 may prevent the evasion of T-cell responses and augment the efficacy of immunotherapies. In a mouse model, for example, Hirano et al showed that B7-H1 expression confers resistance to therapeutic anti-CD137 antibody in mice with established tumors.

In two histologically distinct mouse tumors B7-H1 conferred resistance to immunotherapy by anti-CD137 mAb. B7-H1 on tumor cells may interact with a receptor on effector T cells and form a "shield" to prevent lysis. However, blockade of B7-H1 by specific mAb rescued the function of therapeutic immunity which led to regression of established mouse tumors. To evaluate whether B7-H1 blockade could be applied to enhance CD137 costimulatory therapy, Brown et al examined the effect of B7-H1 mAb in the resistance of B7-H1 tumors; 10B5 is a hamster mAb specific against mouse B7-H1 and is capable of blocking the binding of B7-H1 to its receptor PD-1. In combination with 2A mAb, growth of B7-H1 tumors were completely inhibited after 10B5 treatment and the mice lived for more than 120 days. However, tumors treated with 2A mAb and control hamster immunoglobulin G grew progressively and the mice eventually died. As expected, the treatment with 10B5 alone did not significantly inhibit tumor growth. The report concludes that blocking B7-H1 could enhance the effect of CD137 costimulatory therapy. Selective blocking of B7-H1 may represent a new opportunity for the improvement of cancer immunotherapy.

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B7-H1: Fast Facts on What You Need to Know

Eugene D. Kwon, MD, Associate Professor of Urology and Associate Professor of Immunology, Mayo Clinic College of Medicine, Rochester, Minnesota, offered insights on the impact of B7-H1.

Q. What mechanisms are involved when B7-H1 expression occurs on the surface of the tumor cell?

Dr. Kwon: B7-H1 basically acts like barbed wire or armor on the surface of the tumor cell. Normally, tissues do not have B7-H1 but tumors have an ability to become mutated and start wearing that armor on their surface. B7-H1 essentially kills off any immune cells that approach it and in that sense the tumor cell is protected against immune responses. Tumor cells thus ward off an attack by killing cells that try to kill them. The key to understanding this is that the cell goes through this process of mutation, aberrantly developing the ability to express or manufacture B7-H1 on its surface.

Q. What specifically is the interaction between B7-H1 and the immune cells?

Dr. Kwon: B7-H1 kills immune cells by contact. When immune cells come into contact with B7-H1 there are receptors associated with B7-H1 that activate a program within the immune cells that kills the immune cells or renders them ineffective. This is the reason why cytokine therapy may not be ineffective in some patients.

Q. What are the broader implications in terms of cytokine therapy and prognosis when B7-H1 is a factor?

Dr. Kwon: Cytokine therapy and other immunotherapies can raise the immune response to attack tumors but they may be largely ineffective in most circumstances because even if you empower the immune system, when the immune cells come into contact with the tumor and B7-H1 they are eliminated or shut down. We think that B7-H1 allows the tumor to grow in an unmolested fashion, untethered by the immune system. That's why B7-H1 seems to correlate with prognosis and tumor progression.

Q. What are the potential ramifications for the use of high-dose interleukin-2?

Dr. Kwon: We think there may be implications and we have generated preliminary data. Fundamentally, the preliminary findings to date have been done on such small numbers of patients that it would be unreasonable to reach a conclusion based on those numbers right now. Our earliest glimpses into the matter suggest that one of the rate-limiting steps in high-dose interleukin-2 might be B7-H1 but we have looked at far too few tissues. We can speculate, however, that it might ultimately prove to be a determinant in the response to high-dose or low-dose interleujin-2 therapy.

Q. Are the animal models suggestive of any type of response to interleukin-2 by blocking B7-H1?

Dr. Kwon: In our mouse models we have demonstrated that we can get a much more impressive response by blocking B7-H1 in conjunction with low-dose interleukin-2 and vaccine therapy.

Q. Is there any research directed toward the use of monoclonal antibodies?

Dr. Kwon: This is investigational but there is great interest in developing the monoclonal antibodies for human usage and at Mayo we are in the process of moving in that direction. Clinical trials could be initiated as early as 18 months from now. We would be administering anti-B7-H1 antibody and, perhaps in combination with interleukin-2, hoping to see more marked tumor regression.

Q. Do you have any indications that B7-H1 may be amenable to the use of the newer molecules found to be effective in renal cell carcinoma, such as sorafenib or sunitinib?

Dr. Kwon: It is too early to know what molecules collaborate with B7-H1. We do not yet know much about what is downstream and upstream from B7-H1. We have recently identified a number of molecules that B7-H1 works in concert with that look like they are also favorable targets and that are also instrumental in controlling kidney cancer progression. More information on these molecules will be presented in the publication of an upcoming manuscript. We do have incredible data. B7-H1 is the first costimulatory molecule that's been linked to solid cancer progression ever. Costimulatory molecules have been studied since 1992 and there were no compelling data to show that the molecules in and of themselves correlated with cancer progression and disease outcome. A more accurate term to use is coregulatory. It is one of the coregulatroy molecules clearly correlated with primary tumor and metastatic disease in thwarting the immune system and promoting cancer progression.

Q. In the overall paradigm of kidney cancer pathways, where would you place B7-H1?

Dr. Kwon: In terms of disease progression, B7-H1 is clearly one of the most supported prognostic markers for kidney cancer and also one of the more favorable targets. What makes B7-H1 very favorable is that it is expressed on tumor cells and is clearly an important negative regulator of immune response. This makes it a favorable and potent target for treatment of kidney cancer. In terms of practicality and logic, B7-H1 is one of the most exciting. I do not think there are other data that come close to the evidence surrounding B7-H1 in terms of its impact on disease progression.

Surgical Strategies to Optimize Outcomes in Isolated Renal Fossa Recurrence Following Nephrectomy

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Widely regarded as a marker for an unfavorable prognosis, isolated renal fossa recurrence after nephrectomy is amenable to surgical extirpation, with durable outcomes in selected patients. Nevertheless, many questions remain, including how to identify suitable candidates for resection, evaluating the appropriateness of intraoperative radiation therapy, and follow-up imaging studies of patients at risk for metastatic disease. This report addresses these issues in providing management guidelines.

Although local recurrence of renal cell carcinoma in the renal fossa is considered rare, its discovery is important because such patients are candidates for surgical resection, possible intraoperative radiation therapy (IORT), imaging to detect occult distant disease, or frequent follow-up for impending metastatic lesions.

The incidence of pure local fossa recurrence ranges widely in the literature from 1% to 37%, with most recent reports suggesting an incidence of approximately 1% to 2%.[1,2] Previous reports tend to include local recurrences in the presence of distant metastatic disease. Because the recurrence of isolated renal fossa following radical nephrectomy is rare, it has been infrequently studied and no standard treatment has been recommended. Nevertheless, the use of surgical extirpation with adjuvant IORT in a growing number of patients suggests how selected patients with isolated local recurrence in the renal fossa may have favorable and durable outcomes following application of these techniques.

It is controversial whether this entity is considered a remnant of microscopic disease or a form of metastatic disease. Historically patients with metastatic renal carcinoma have a poor prognosis, with the majority dying within 2 years of diagnosis and a 5-year survival rate of approximately 10%.[3-5]

Although the literature is relatively sparse, there have been a few case series of the treatment of local recurrence of kidney cancer. In some of these reports, the study population is heterogeneous and includes patients with renal malignancies that are not renal cell carcinoma.[6] In other series, the authors have focused on patients with local-regional recurrences, including lymph node recurrences or the presence of resected distant metastatic disease, or in some cases no malignancy found on exploration.[7]

The importance of an aggressive approach in patients with isolated local recurrence in the renal fossa has been highlighted by several studies. Results from the University of California, San Francisco, serve as a good indication of how such recurrent lesions, although challenging, can be effectively managed.[8] Unlike many of the previous reports, our study focused on a homogeneous population—only on patients with recurrence of renal cell carcinoma in the renal fossa. A total of 14 patients were treated for this lesion between 1990 and 2003; mean time to recurrence was 40 months. Mean size of the recurrent tumor was 6.35 cm; 9 patients died of progressive, metastatic disease after a mean of 17 months and 5 are alive with a mean survival of 66 months. Following nephrectomy, the time to recurrence approached statistical significance (P = .06) when patients who were alive were compared with those who had died. The size of the recurrent mass did not differ statistically between these two groups.

Adjuvant IORT was not associated with a difference in survival rates. Local fossa recurrence developed in 2 patients. Survival was 40% at 2 years and 30% at 5 years after surgery; 42% of the patients experienced complications and no perioperative mortality occurred.

Significance of Isolated Fossa Recurrence

When detected, isolated fossa recurrence should be considered a marker for an unfavorable prognosis.8 Concurrent metastatic disease may be present and all patients should undergo systemic imaging. As early as 1978, this prognosis became apparent when de Kernion et al compared survival

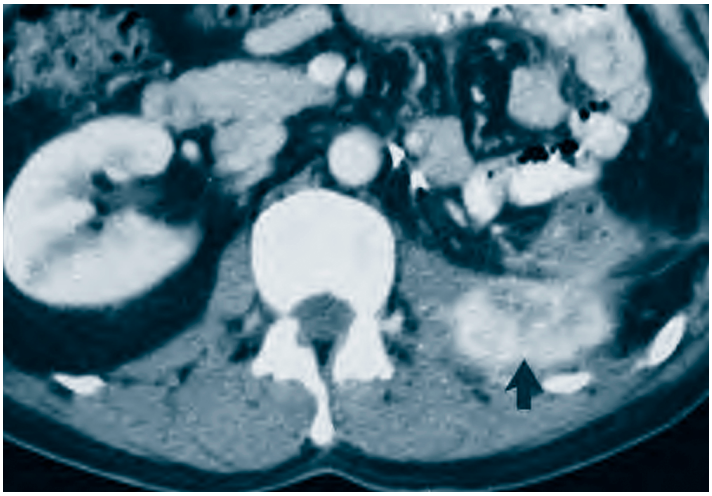
of patients with metastatic renal cell carcinoma with no local recurrence to that of patients who had recurrence within the renal fossa and found that 86% with local recurrence died within 1 year versus a 40% survival rate with metastases and no local recurrence.[9] Since the publication of that study, however, only a handful of reports have examined treatment for local recurrence of kidney cancer. One of the limitations in getting a definitive picture of treatment in this setting is that most of the series reported in the last two decades include patients with other renal malignancies, such as spindle cell carcinoma or transitional cell carcinoma. These malignancies have different biological behaviors than renal cell carcinoma. These series also included patients who may have been previously treated for distant metastatic disease. The heterogeneity of these patient populations tends to make interpretation of the literature problematic. Our series, however, resolves this issue because it focused on a well-described homogeneous population with pure local recurrence of renal cell carcinoma. In contrast to other studies, it also examined the potential benefit of a single mode of adjuvant IORT.

Our series and previous reports agree on a number of points:

- Tumor stage at initial radical nephrectomy can vary widely. Schrödter et al, Itano et al, and Gogus demonstrated a substantial number of T1 cases and even low-risk T1 cases may develop local recurrence.[1,4,7] This highlights the importance of meticulous surgical technique at the time of initial nephrectomy to prevent local recurrence.
- Local recurrence has been reported with all histological subtypes, as well as with all Fuhrman grades of tumor. Despite significant biological heterogeneity of tumor, current risk stratification does not reflect such diversity. There is a need to more accurately assign risk, perhaps using novel molecular markers and other markers of tissue invasion instead of metastatic spread by lymphovascular migration.
- No study has shown the importance of length of time from radical nephrectomy to local recurrence as a significant factor. Although patients with late local recurrences tend to survive longer, no data have suggested a statistically significant difference in the interval. Nevertheless, a trend to statistical significance has been noted in each of the recent studies (P =~ .06). It may be that patients with late local recurrences have an indolent growth pattern, are more amenable to surgery, and were less likely to have had micrometastatic disease at presentation.
- Adjuvant therapy does not appear to increase survival.[1,7] The 5-year survival data in our study (30%) were similar to the 28% observed by Itano et al, also over 5 years.[1]

Role of IORT

Although results with IORT in our study and in a randomized trial performed by the National Cancer Institute (NCI) have not demonstrated a decisive advantage to the use of such treatment, we believe IORT should be included, selectively, in the management of renal cell recurrences. A formal statistical subset analysis was not possible in our series because there were only a few patients studied. Although no difference in survival was noted due to adjuvant IORT, the NCI experience with use of radiation therapy in retroperitoneal sarcomas supports its application and conforms to the rationale that patients with large recurrent local renal fossa tumors may benefit from additional postoperative external beam radiation therapy.



Locally recurrent renal cell carcinoma as seen in contrast-enhanced helical CT. CT scan of 46-year-old man with recurrent renal cell carcinoma who underwent left nephrectomy reveals enhancing mass (arrow) that invaded left psoas and quadratus lumborum muscles. (Scatarige JC, Sheth S, Corl FM. Patterns of recurrence in renal cell carcinoma: manifestations on helical CT. *Am J Roentgenol*. 2001; 177:653-658)

Sindelar et al did not demonstrate a difference in survival with the addition of IORT, but there was an improvement in local control from 20% to 60% with the addition of IORT.[10] Thirty-five patients with surgically resected sarcomas of the retroperitoneum were enrolled in a prospective, randomized, clinical trial comparing 20 Gy intraoperative radiotherapy in combination with postoperative low-dose (35 to 40 Gy) external-beam radiotherapy with postoperative high-dose (50 to 55 Gy) external-beam radiotherapy alone. Chemotherapy with doxorubicin hydrochloride, cyclophosphamide (anhydrous), and methotrexate sodium was used for a portion of the trial. Fifteen patients who received intraoperative radiotherapy and 20 control patients were followed up for a minimum of 5 years (median follow-up, 8 years). Median survival times were similar for the group that received intraoperative radiotherapy (45 months) and the control group (52 months).

There were no indications of benefit from adjunctive chemotherapy. The number of locoregional recurrences was significantly lower among those who received intraoperative radiotherapy (6 of 15) than control patients (16 of 20). Patients who received intraoperative radiotherapy had fewer complications of disabling radiation-related enteritis (2 of 15) than control patients (10 of 20), but radiation-related peripheral neuropathy was more frequent among those who received intraoperative radiotherapy (9 of 15) than among control patients (1 of 20). The significantly lower number of locoregional recurrences would be likely to improve quality of life in this patient group, and this favorable effect has contributed to our rationale for using IORT. Although the

potential benefit is difficult to quantify, we routinely consider its use.

Long-term Survival Following Resection

Evidence that the poor survival rates associated with isolated local recurrence can be altered with careful surgical resection emerged from the study by Itano et al, who followed 30 patients in whom recurrence was identified after complete radical nephrectomy and without evidence of metastatic disease.[1] Patients with any nodal involvement at radical nephrectomy were excluded from the study as were those who had undergone any form of partial nephrectomy. Patients were divided into three treatment groups: (1) 9 patients undergoing observation, (2) 11 undergoing therapy excluding surgical extirpation, and (3) 10 in whom complete surgical resection alone or in conjunction with additional therapy was done.

Survival rates among symptomatic and asymptomatic patients were not significantly different during the mean follow-up of 3.3 years. Significantly, the 5-year survival rate with surgical resection was 51% compared to 18% treated with adjuvant medical therapy and only 13% with observation alone. Additionally, there was no correlation among original T stage, grade, or tumor size and survival. Similar to Esrig et al,[6] we were unable to document a statistical correlation between the disease-free interval and outcome. We did find a positive correlation between the median time from nephrectomy to development of local recurrence and survival that was highly suggestive but did not achieve statistical significance.

The two significant prognostic factors determined in this study were surgical resection and a greater time to development of fossa recurrence. Among operative candidates median disease-free interval was greater than for those not offered surgery, likely reflecting a strong selection bias. However, multivariate analysis directly comparing the two variables showed that the longer disease-free interval did not solely account for the difference in survival. Additionally, there did not appear to be a significant difference in comorbidities. On the basis of their observations, Itano et al[1] concluded:

- The isolated recurrence of renal cell carcinoma in the renal bed may behave as a solitary metastasis and that select patients may benefit from surgical resection.
- Surgical resection of isolated renal cell carcinoma fossa recurrence with or without radiation should be considered in a patient with an acceptable comorbidity index and when it has been more than 1 year since nephrectomy.
- While the complication rate was significant, earlier recognition of fossa recurrence may prove to be more responsive to aggressive treatment.

In an elucidation of the role of resection of solitary metastases from renal cell carcinoma and a further analysis of long-term survival, Kavolius et al documented a 5-year survival rate of 35% to 50%.[5] This retrospective analysis reviewed the course of 278 patients with recurrent renal cell carcinoma: 141 underwent a curative metastectomy for their first recurrence (44% 5-year overall survival [OS] rate), 70 patients underwent noncurative surgery (14% 5-year OS), and 67 patients were treated nonsurgically (11% 5-year OS). Favorable features for survival were:

- A disease-free interval greater than 12 months vs 12 months or less (55% vs 9% 5-year OS; $P < .0001$)
- Solitary vs multiple sites of metastases (54% vs 29% 5-year OS)
- Age younger than 60 years (49% vs 35% 5-year OS)

Favorable predictors of survival included a single site of first recurrence, curative resection of first metastasis, a long disease-free interval, a solitary site of first metastasis, and a metachronus presentation with recurrence. Thus, selected patients with recurrent renal cell carcinoma who are candidates for curative resection of their disease have a greater likelihood of long-term survival, especially with a single site of recurrence and/or a long disease-free interval.

Radiofrequency Ablation: Potential Option in Unresectable Cases

Comorbidities and tumor location may preclude the use of surgery in some patients with isolated local recurrence of renal cell carcinoma after radical nephrectomy. In such cases radiofrequency ablation or cryoablation may be alternative options for treating small, focal malignancies. McLaughlin et al reported their findings in a 61-year-old patient who, following the use of radiofrequency ablation, did not show radiographic evidence of malignancy 16 months after the technique was used.[11] After nephrectomy the patient had been followed at approximately 6-month intervals with computed tomographic (CT) studies and had no evidence of recurrence or metastatic disease for 4 years. But at 52 months CT scans revealed a 5.5 x 7.0 cm heterogeneously enhancing mass in the region of the left renal fossa.

In the 16 months after ablation, CT studies were conducted every 3 months. At 6 weeks after the procedure the CT scan revealed a reduction in the size of the mass to 4.8 x 3.8 cm and the absence of enhancement within the mass. A further decrease occurred at 14 months, as well as at 16 months with a continued absence of enhancement. At that point there had been no evidence of recurrence or metastases, and the patient remained asymptomatic. Radiographic findings of no contrast enhancement and tumor shrinkage or stability are promising signs and have been shown to correlate with histologic findings of complete tumor ablation.[12] On a cautionary note, however, McLaughlin et al suggest further study is needed to identify which patients would be the best candidates for this technique and as an alternative to surgery.[11] Guidelines are still needed on identifying the criteria for which patients should undergo ablation and data are needed to determine the long-term efficacy of this modality before it can be recommended as an alternative to aggressive surgical treatment.

Value of FDG-PET in Distant Metastases from Renal Cell Carcinoma

As isolated renal fossa recurrence may be an indicator of impending metastases, sensitive and specific imaging needs to be carried out. Histologic evaluation is the gold standard for confirming presence of malignancy in sites of suspected disease. Computed tomography is the imaging modality cur-

rently used to stage and detect distant metastases in patients with renal cell carcinoma. The overall accuracy of CT studies for staging renal cell carcinoma ranges from 61% to 91%.[13-15] Subcentimeter pulmonary nodules are frequently seen in patients with suspected advanced disease; however, they may be nonmalignant and represent granulomas or other benign structures. Improving the diagnostic yield of these investigations while precluding the need for obtaining a tissue diagnosis would have obvious implications in management.

F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) has been shown to complement conventional anatomic imaging modalities in staging and detecting distant disease for many cancer sites.[16-20] The role of FDG-PET in the staging and detection of distant metastases from renal cell carcinoma has not been clearly established. Majhail et al studied the role of FDG-PET in the evaluation of distant metastases from renal cell carcinoma.[21] Twenty-four patients with histologically proven clear-cell renal cell carcinoma undergoing surgical evaluation for possible resection of recurrent disease were investigated. All patients had suspected distant metastases based on conventional anatomic imaging techniques (CT and magnetic resonance imaging). A total of 36 distant metastatic sites were identified.

Histologically documented distant metastases from renal cell carcinoma were present in 33 sites (21 patients). Overall sensitivity, specificity, and positive predictive value of FDG-PET for the detection of distant metastases were 63.6% (21 of 33), 100% (3 of 3), and 100% (21 of 21), respectively. The mean size of distant metastases in patients with true-positive FDG-PET was 2.2 cm (95% CI, 1.7 to 2.6 cm) compared with 1.0 cm in patients with false-negative FDG-PET (95% CI, 0.7 to 1.4 cm; $P = .001$).

Majhail et al conclude that FDG-PET may be useful as an imaging modality complementary to computed tomography in the evaluation of distant metastases from renal cell carcinoma, especially for lesions greater than 1.5 cm in size.[21] In patients with metastatic disease identified by anatomic radiologic imaging techniques, a positive FDG-PET scan, particularly for large lesions (greater than 1.5 cm), could obviate the need for pathologic confirmation of disease. However, FDG-PET may not accurately characterize small lesions (less than 1.0 cm). Depending on the clinical scenario, biopsy is needed to evaluate for the presence of metastatic renal cell carcinoma in such lesions, especially if the FDG-PET scan is negative. Overall, FDG-PET scintigraphy is not a very sensitive imaging modality for the evaluation of metastatic renal cell carcinoma, particularly with regard to small lesions. However, positive FDG-PET is predictive for the presence of renal cell carcinoma in lesions imaged, may complement anatomic radiologic imaging modalities, and may alleviate the need for a biopsy in selected situations. A negative FDG-PET study, however, does not rule out active malignancy. The role of FDG-PET in other histologic types of renal cell carcinoma and for staging patients with the disease needs to be further explored and validated in clinical trials. Further study is needed to delineate the role of FDG-PET specifically in patients with isolated renal fossa following nephrectomy.

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Report Card on Adjuvant Therapy: Trials Build Enrollment, Enhancing Prospects for New Treatment Options

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Expectations are high that this will finally be the year when progress is made toward developing adjuvant therapy options. It is a good time for a progress report on how far we have come, where things stand, and what the future may bring.

While mortality rates from prostate and bladder cancers hover around 20%, the mortality rate from renal cell carcinoma (RCC) is greater than 40%. RCC occurs about twice as often in men as in women. It is the seventh leading type of cancer among men and the tenth cause of cancer mortality, accounting for about 3% of new cancers and cancer deaths. The American Cancer Association projected 36,160 new cancers of the kidney or renal pelvis in 2005 in the Unites States and 12,660 deaths.[1] Although the diagnosis of RCC is increasing at about 1.5% annually, survival rates have not changed significantly in decades.[2]

The majority of patients, about 70%, present with localized or locally advanced disease. These patients are potentially curable by nephrectomy, but recurrence rates for patients with locally aggressive tumors range from 35% to 65%, depending on individual status. Although mortality rates associated with RCCs remain among the highest of all urological cancers, a current round of Phase 3 clinical trials and new staging systems incorporating molecular markers are widely expected to change the paradigm for long-term management of RCC. Expectations are high that during the first quarter of 2006, two new agents will be approved by the FDA and added to the armamentarium of therapies for advanced renal cell cancer. Trials are in an advanced state of planning that will discover whether these agents may be useful in the adjuvant setting. The shift cannot come too soon.

Unlike many cancers, RCC is generally not responsive to postoperative adjuvant therapies. Postoperative hormonal treatment, radiation, and nonspecific cytokine therapy have all failed to show any clinical benefit in trials with patients who have resected high-risk locally advanced RCC.[3] Trials with some hormonal agents[4] and cytokine agents[5] showed a negative impact on overall survival when used as adjuvant therapy. A trial with high-dose interleukin-2 (IL-2), the only systemic therapy currently approved for RCC by the FDA, was halted early for lack of efficacy as an adjuvant therapy.[6]

Despite disappointing trial results, the weeks following nephrectomy would appear to provide a unique window for treatment. The residual tumor mass is at its lowest possible point, typically reduced to microscopic volume. The patient's immune system, although stressed from combating the growing tumor, has been given a significant respite by resection of the primary tumor mass and the most likely secondary sites. Growing knowledge of the detailed molecular genetics that underlie RCC holds hope for the development of treatment strategies based on novel diagnostic and prognostic markers, novel therapeutics that have entered late stage clinical trials, and personalized vaccines in all stages of development[3].

Glimmers of Efficacy

The concept of adjuvant therapy, systematically treating patients at high risk of metastatic disease following surgical resection of the primary tumor, is a familiar one. It has been used successfully in a variety of cancers, including breast, lung, and colon cancer. Adjuvant therapy has not developed as a full-fledged alternative in RCC for three primary reasons:

- There are two FDA-approved systemic treatment for metastatic RCC, high-dose IL-2, and sorafenib (Nexavar®). They have not been studied as intensively as systemic treatments for other types of metastatic cancers.
- Second, agents currently available for adjuvant therapy of metastatic RCC have poor toxicity profiles.
- Finally, RCC is a relatively rare cancer, seventh in incidence among men and even less frequent in women. The relatively low numbers of patients makes accrual for large randomized trials a slow process.[3]

Three general types of adjuvant therapy, radiation, hormonal, and biologic, have undergone study. All three have provided meager to negative results. Adjuvant radiation therapy to the kidney bed following radical nephrectomy for stage II or III cancer was attempted in Scandinavia in the 1980s. In one of the largest trials, 72 patients were randomized to receive postoperative radiotherapy or no further

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PROLEUKIN® administration should be withheld in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

1. PROLEUKIN® [prescribing information]. Emeryville, Calif: Chiron Corporation; 2000. Overall response rates (complete and partial) were 16% for metastatic melanoma and 15% for metastatic renal cell carcinoma.
2. Median duration not yet observed; a conservative value is presented, which represents the minimum median duration of response.

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PROLEUKIN administration should be withheld in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

DESCRIPTION

PROLEUKIN® (aldesleukin) for injection, a human recombinant interleukin-2 product, is a highly purified protein with a molecular weight of approximately 15,300 daltons. The chemical name is des-alanyl-1, serine-125 human interleukin-2. PROLEUKIN, a lymphokine, is produced by recombinant DNA technology using a genetically engineered *E. coli* strain containing an analog of the human interleukin-2 gene. Genetic engineering techniques were used to modify the human IL-2 gene, and the resulting expression clone encodes a modified human interleukin-2. This recombinant form differs from native interleukin-2 in the following ways: a) PROLEUKIN is not glycosylated because it is derived from *E. coli* ; b) the molecule has no N-terminal alanine; the codon for this amino acid was deleted during the genetic engineering procedure; c) the molecule has serine substituted for cysteine at amino acid position 125; this was accomplished by site specific manipulation during the genetic engineering procedure; and d) the aggregation state of PROLEUKIN is likely to be different from that of native interleukin-2.

The *in vitro* biological activities of the native nonrecombinant molecule have been reproduced with PROLEUKIN.[1,2]

PROLEUKIN is supplied as a sterile, white to off-white, lyophilized cake in single-use vials intended for intravenous (IV) administration. When reconstituted with 1.2 mL Sterile Water for Injection, USP, each mL contains 18 million IU (1.1 mg) PROLEUKIN, 50 mg mannitol, and 0.18 mg sodium dodecyl sulfate, buffered with approximately 0.17 mg monobasic and 0.89 mg dibasic sodium phosphate to a pH of 7.5 (range 7.2 to 7.8). The manufacturing process for PROLEUKIN involves fermentation in a defined medium containing tetracycline hydrochloride. The presence of the antibiotic is not detectable in the final product. PROLEUKIN contains no preservatives in the final product.

PROLEUKIN biological potency is determined by a lymphocyte proliferation bioassay and is expressed in International Units (IU) as established by the World Health Organization 1st International Standard for Interleukin-2 (human). The relationship between potency and protein mass is as follows:

18 million (18 x 10^6) IU PROLEUKIN = 1.1 mg protein

CLINICAL PHARMACOLOGY

PROLEUKIN® (aldesleukin) has been shown to possess the biological activities of human native interleukin-2.[1,2] *In vitro* studies performed on human cell lines demonstrate the immunoregulatory properties of PROLEUKIN, including: a) enhancement of lymphocyte mitogenesis and stimulation of long-term growth of human interleukin-2 dependent cell lines; b) enhancement of lymphocyte cytotoxicity; c) induction of killer cell (lymphokine-activated (LAK) and natural (NK)) activity; and d) induction of interferon-gamma production.

The *in vivo* administration of PROLEUKIN in animals and humans produces multiple immunological effects in a dose dependent manner. These effects include activation of cellular immunity with profound lymphocytosis, eosinophilia, and thrombocytopenia, and the production of cytokines including tumor necrosis factor, IL-1 and gamma interferon.[3] *In vivo* experiments in murine tumor models have shown inhibition of tumor growth.[4] The exact mechanism by which PROLEUKIN mediates its antitumor activity in animals and humans is unknown.

Pharmacokinetics: PROLEUKIN exists as biologically active, non-covalently bound microaggregates with an average size of 27 recombinant interleukin-2 molecules. The solubilizing agent, sodium dodecyl sulfate, may have an effect on the kinetic properties of this product.

The pharmacokinetic profile of PROLEUKIN is characterized by high plasma concentrations following a short IV infusion, rapid distribution into the extravascular space and elimination from the body by metabolism in the kidneys with little or no bioactive protein excreted in the urine. Studies of IV PROLEUKIN in sheep and humans indicate that upon completion of infusion, approximately 30% of the administered dose is detectable in plasma. This finding is consistent with studies in rats using radiolabeled PROLEUKIN, which demonstrate a rapid (<1 min) uptake of the majority of the label into the lungs, liver, kidney, and spleen.

The serum half-life (T 1/2) curves of PROLEUKIN remaining in the plasma are derived from studies done in 52 cancer patients following a 5-minute IV infusion. These patients were shown to have a distribution and elimination T 1/2 of 13 and 85 minutes, respectively.

Following the initial rapid organ distribution, the primary route of clearance of circulating PROLEUKIN is the kidney. In humans and animals, PROLEUKIN is cleared from the circulation by both glomerular filtration and peritubular extraction in the kidney.[5-6] This dual mechanism for delivery of PROLEUKIN to the proximal tubule may account for the preservation of clearance in patients with rising serum creatinine values. Greater than 80% of the amount of PROLEUKIN distributed to plasma, cleared from the circulation and presented to the kidney is metabolized to amino acids in the cells lining the proximal convoluted tubules. In humans, the mean clearance rate in cancer patients is 268 mL/min.

The relatively rapid clearance of PROLEUKIN has led to dosage schedules characterized by frequent, short infusions. Observed serum levels are proportional to the dose of PROLEUKIN.

Immunogenicity: Fifty-seven of 77 (74%) metastatic renal cell carcinoma patients treated with an every 8-hour PROLEUKIN regimen and 33 of 50 (66%) metastatic melanoma patients treated with a variety of IV regimens developed low titers of non-neutralizing anti-PROLEUKIN antibodies. Neutralizing antibodies were not detected in this group of patients, but have been detected in 1/106 (<1%) patients treated with IV PROLEUKIN using a wide variety of schedules and doses. The clinical significance of anti-PROLEUKIN antibodies is unknown.

Clinical Experience: Two hundred fifty-five patients with metastatic renal cell cancer (metastatic RCC) were treated with single agent PROLEUKIN in 7 clinical studies conducted at 21 institutions. Two hundred seventy patients with metastatic melanoma were treated with single agent PROLEUKIN in 8 clinical studies conducted at 22 institutions. Patients enrolled in trials of single agent PROLEUKIN were required to have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 and normal organ function as determined by cardiac stress test, pulmonary function tests, and creatinine ≤1.5 mg/dL. Patients with brain metastases, active infections, organ allografts and diseases requiring steroid treatment were excluded.

PROLEUKIN was given by 15 min IV infusion every 8 hours for up to 5 days (maximum of 14 doses). No treatment was given on days 6 to 14 and then dosing was repeated for up to 5 days on days 15 to 19 (maximum of 14 doses). These 2 cycles constituted 1 course of therapy. Patients could receive a maximum of 28 doses during a course of therapy. In practice >90% of patients had doses withheld. Metastatic RCC patients received a median of 20 of 28 scheduled doses of PROLEUKIN. Metastatic melanoma patients received a median of 18 of 28 scheduled doses of PROLEUKIN during the first course of therapy. Doses were withheld for specific toxicities (See "**DOSAGE AND ADMINISTRATION**" section, "**Dose Modifications**" subsection and "**ADVERSE REACTIONS**" section).

In the renal cell cancer studies (n=255), objective response was seen in 37 (15%) patients, with 17 (7%) complete and 20 (8%) partial responders (See Table I). The 95% confidence interval for objective response was 11% to 20%. Onset of tumor regression was observed as early as 4 weeks after completion of the first course of treatment, and in some cases, tumor regression continued for up to 12 months after the start of treatment. Responses were observed in both lung and non-lung sites (e.g., liver, lymph node, renal bed occurrences, soft tissue). Responses were also observed in patients with individual bulky lesions and high tumor burden.

In the metastatic melanoma studies (n=270), objective response was seen in 43 (16%) patients, with 17 (6%) complete and 26 (10%) partial responders (See Table I). The 95% confidence interval for objective response was 12% to 21%. Responses in metastatic melanoma patients were observed in both visceral and non-visceral sites (e.g., lung, liver, lymph node, soft tissue, adrenal, subcutaneous). Responses were also observed in patients with individual bulky lesions and large cumulative tumor burden.

TABLE I: PROLEUKIN CLINICAL RESPONSE DATA

	Number of Responding Patients (response rate)	Median Response Duration in Months (range)
Metastatic RCC		
CR's	17 (7%)	80+* (7 to 131+)
PR's	20 (8%)	20 (3 to 126+)
PR's + CR's	37 (15%)	54 (3 to 131+)
Metastatic Melanoma		
CR's	17 (6%)	59+* (3 to 122+)
PR's	26 (10%)	6 (1 to 111+)
PR's + CR's	43 (16%)	9 (1 to 122+)

(+) sign means ongoing

*Median duration not yet observed; a conservative value is presented which represents the minimum median duration of response.

An analysis of prognostic factors showed that a better ECOG performance status (see Table II) was significantly associated with response.

TABLE II: PROLEUKIN CLINICAL RESPONSE BY ECOG PERFORMANCE STATUS (PS)

Pretreatment	METASTATIC RCC		METASTATIC MELANOMA	
ECOG PS	CR	PR	CR	PR
0	14/166 (8%)	16/166 (10%)	14/191 (7%)	22/191 (12%)
≥1	3/89 (3%)	4/89 (4%)	3/79 (4%)	4/79 (5%)

INDICATIONS AND USAGE

PROLEUKIN® (aldesleukin) is indicated for the treatment of adults with metastatic renal cell carcinoma (metastatic RCC).

PROLEUKIN is indicated for the treatment of adults with metastatic melanoma.

Careful patient selection is mandatory prior to the administration of PROLEUKIN. See "**CONTRAINDICATIONS**", "**WARNINGS**" and "**PRECAUTIONS**" sections regarding patient screening, including recommended cardiac and pulmonary function tests and laboratory tests.

Evaluation of clinical studies to date reveals that patients with more favorable ECOG performance status (ECOG PS 0) at treatment initiation respond better to PROLEUKIN, with a higher response rate and lower toxicity (See "**CLINICAL PHARMACOLOGY**" section, "**Clinical Experience**" subsection and "**ADVERSE REACTIONS**" section). Therefore, selection of patients for treatment should include assessment of performance status.

Experience in patients with ECOG PS >1 is extremely limited.

CONTRAINDICATIONS

PROLEUKIN® (aldesleukin) is contraindicated in patients with a known history of hypersensitivity to interleukin-2 or any component of the PROLEUKIN formulation.

PROLEUKIN is contraindicated in patients with an abnormal thallium stress test or abnormal pulmonary function tests and those with organ allografts. Retreatment with PROLEUKIN is contraindicated in patients who have experienced the following drug-related toxicities while receiving an earlier course of therapy:

- Sustained ventricular tachycardia (≥ 5 beats)
- Cardiac arrhythmias not controlled or unresponsive to management
- Chest pain with ECG changes, consistent with angina or myocardial infarction
- Cardiac tamponade
- Intubation for >72 hours
- Renal failure requiring dialysis >72 hours
- Coma or toxic psychosis lasting >48 hours
- Repetitive or difficult to control seizures
- Bowel ischemia/perforation
- GI bleeding requiring surgery

WARNINGS

See boxed "**WARNINGS**"

Because of the severe adverse events which generally accompany PROLEUKIN® (aldesleukin) therapy at the recommended dosages, thorough clinical evaluation should be performed to identify patients with significant cardiac, pulmonary, renal, hepatic, or CNS impairment in whom PROLEUKIN is contraindicated. Patients with normal cardiovascular, pulmonary, hepatic, and CNS function may experience serious, life threatening or fatal adverse events. Adverse events are frequent, often serious, and sometimes fatal.

Should adverse events, which require dose modification occur, dosage should be withheld rather than reduced (See "**DOSAGE AND ADMINISTRATION**" section, "**Dose Modifications**" subsection).

PROLEUKIN has been associated with exacerbation of pre-existing or initial presentation of autoimmune disease and inflammatory disorders. Exacerbation of Crohn's disease, scleroderma, thyroiditis, inflammatory arthritis, diabetes mellitus, oculo-bulbar myasthenia gravis, crescentic IgA glomerulonephritis, cholecystitis, cerebral vasculitis, Stevens-Johnson syndrome and bullous pemphigoid, has been reported following treatment with IL-2.

All patients should have thorough evaluation and treatment of CNS metastases and have a negative scan prior to receiving PROLEUKIN therapy. New neurologic signs, symptoms, and anatomic lesions following PROLEUKIN therapy have been reported in patients without evidence of CNS metastases. Clinical manifestations included changes in mental status, speech difficulties, cortical blindness, limb or gait ataxia, hallucinations, agitation, obtundation, and coma. Radiological findings included multiple and, less commonly, single cortical lesions on MRI and evidence of demyelination. Neurologic signs and symptoms associated with PROLEUKIN therapy usually improve after discontinuation of PROLEUKIN therapy; however, there are reports of permanent neurologic defects. One case of possible cerebral vasculitis, responsive to dexamethasone, has been reported. In patients with known seizure disorders, extreme caution should be exercised as PROLEUKIN may cause seizures.

PRECAUTIONS

General: Patients should have normal cardiac, pulmonary, hepatic, and CNS function at the start of therapy. (See "**PRECAUTIONS**" section, "**Laboratory Tests**" subsection). Capillary leak syndrome (CLS) begins immediately after PROLEUKIN® (aldesleukin) treatment starts and is marked by increased capillary permeability to protein and fluids and reduced vascular tone. In most patients, this results in a concomitant drop in mean arterial blood pressure within 2 to 12 hours after the start of treatment. With continued therapy, clinically significant hypotension (defined as systolic blood pressure below 90 mm Hg or a 20 mm Hg drop from baseline systolic pressure) and hypoperfusion will occur. In addition, extravasation of protein and fluids into the extravascular space will lead to the formation of edema and creation of new effusions.

Medical management of CLS begins with careful monitoring of the patient's fluid and organ perfusion status. This is achieved by frequent determination of blood pressure and pulse, and by monitoring organ function, which includes assessment of mental status and urine output. Hypovolemia is assessed by catheterization and central pressure monitoring.

Flexibility in fluid and pressor management is essential for maintaining organ perfusion and blood pressure. Consequently, extreme caution should be used in treating patients with fixed requirements for large volumes of fluid (e.g., patients with hypercalcemia). Administration of IV fluids, either colloids or crystalloids is recommended for treatment of hypovolemia. Correction of hypovolemia may require large volumes of IV fluids but caution is required because unrestrained fluid administration may exacerbate problems associated with edema formation or effusions. With extravascular fluid accumulation, edema is common and ascites, pleural or pericardial effusions may develop. Management of these events depends on a careful balancing of the effects of fluid shifts so that neither the consequences of hypovolemia (e.g., impaired organ perfusion) nor the consequences of fluid accumulations (e.g., pulmonary edema) exceed the patient's tolerance.

Clinical experience has shown that early administration of dopamine (1 to 5 µg/kg/min) to patients manifesting capillary leak syndrome, before the onset of hypotension, can help to maintain organ perfusion particularly to the kidney and thus preserve urine output. Weight and urine output should be carefully monitored. If organ perfusion and blood pressure are not sustained by dopamine therapy, clinical investigators have increased the dose of dopamine to 6 to 10 µg/kg/min or have added phenylephrine hydrochloride (1 to 5 µg/kg/min) to low dose dopamine (See "**ADVERSE REACTIONS**" section). Prolonged use of pressors, either in combination or as individual agents, at relatively high doses, may be associated with cardiac rhythm disturbances. If there has been excessive weight gain or edema formation, particularly if associated with shortness of breath from pulmonary congestion, use of diuretics, once blood pressure has normalized, has been shown to hasten recovery. **NOTE: Prior to the use of any product mentioned, the physician should refer to the package insert for the respective product.**

PROLEUKIN® (aldesleukin) treatment should be withheld for failure to maintain organ perfusion as demonstrated by altered mental status, reduced urine output, a fall in the systolic blood pressure below 90 mm Hg or onset of cardiac arrhythmias (See "**DOSAGE AND ADMINISTRATION**" section, "**Dose Modifications**" subsection). Recovery from CLS begins soon after cessation of PROLEUKIN therapy. Usually, within a few hours, the blood pressure rises, organ perfusion is restored and reabsorption of extravasated fluid and protein begins.

Kidney and liver function are impaired during PROLEUKIN treatment. Use of concomitant nephrotoxic or hepatotoxic medications may further increase toxicity to the kidney or liver.

Mental status changes including irritability, confusion, or depression which occur while receiving PROLEUKIN may be indicators of bacteremia or early bacterial sepsis, hypoperfusion, occult CNS malignancy, or direct PROLEUKIN-induced CNS toxicity. Alterations in mental status due solely to PROLEUKIN therapy may progress for several days before recovery begins. Rarely, patients have sustained permanent neurologic deficits (See "**PRECAUTIONS**" section "**Drug Interactions**" subsection).

Exacerbation of pre-existing autoimmune disease or initial presentation of autoimmune and inflammatory disorders has been reported following PROLEUKIN alone or in combination with interferon (See "**PRECAUTIONS**" section "**Drug Interactions**" subsection and "**ADVERSE REACTIONS**" section). Hypothyroidism, sometimes preceded by hyperthyroidism, has been reported following PROLEUKIN treatment. Some of these patients required thyroid replacement therapy. Changes in thyroid function may be a manifestation of autoimmunity. Onset of symptomatic hyperglycemia and/or diabetes mellitus has been reported during PROLEUKIN therapy.

PROLEUKIN enhancement of cellular immune function may increase the risk of allograft rejection in transplant patients.

Laboratory Tests: The following clinical evaluations are recommended for all patients, prior to beginning treatment and then daily during drug administration.

- Standard hematologic tests-including CBC, differential and platelet counts
- Blood chemistries-including electrolytes, renal and hepatic function tests
- Chest x-rays

Serum creatinine should be ≤1.5 mg/dL prior to initiation of PROLEUKIN treatment.

All patients should have baseline pulmonary function tests with arterial blood gases. Adequate pulmonary function should be documented (FEV_1 >2 liters or ≥75% of predicted for height and age) prior to initiating therapy.

All patients should be screened with a stress thallium study. Normal ejection fraction and unimpaired wall motion should be documented. If a thallium stress test suggests minor wall motion abnormalities further testing is suggested to exclude significant coronary artery disease.

Daily monitoring during therapy with PROLEUKIN should include vital signs (temperature, pulse, blood pressure, and respiration rate), weight, and fluid intake and output. In a patient with a decreased systolic blood pressure, especially less than 90 mm Hg, constant cardiac rhythm monitoring should be conducted. If an abnormal complex or rhythm is seen, an ECG should be performed. Vital signs in these hypotensive patients should be taken hourly.

During treatment, pulmonary function should be monitored on a regular basis by clinical examination, assessment of vital signs and pulse oximetry. Patients with dyspnea or clinical signs of respiratory impairment (tachypnea or rales) should be further assessed with arterial blood gas determination. These tests are to be repeated as often as clinically indicated.

Cardiac function should be assessed daily by clinical examination and assessment of vital signs. Patients with signs or symptoms of chest pain, murmurs, gallops, irregular rhythm or palpitations should be further assessed with an ECG examination and cardiac enzyme evaluation. Evidence of myocardial injury, including findings compatible with myocardial infarction or myocarditis, has been reported. Ventricular hypokinesia due to myocarditis may be persistent for several months. If there is evidence of cardiac ischemia or congestive heart failure, PROLEUKIN therapy should be held, and a repeat thallium study should be done.

Drug Interactions: PROLEUKIN may affect central nervous function. Therefore, interactions could occur following concomitant administration of psychotropic drugs (e.g., narcotics, analgesics, antiemetics, sedatives, tranquilizers).

Concurrent administration of drugs possessing nephrotoxic (e.g., aminoglycosides, indomethacin), myelotoxic (e.g., cytotoxic chemotherapy), cardiotoxic (e.g., doxorubicin) or hepatotoxic (e.g., methotrexate, asparaginase) effects with PROLEUKIN may increase toxicity in these organ systems. The safety and efficacy of PROLEUKIN in combination with any antineoplastic agents have not been established.

In addition, reduced kidney and liver function secondary to PROLEUKIN treatment may delay elimination of concomitant medications and increase the risk of adverse events from those drugs.

Hypersensitivity reactions have been reported in patients receiving combination regimens containing sequential high dose PROLEUKIN and antineoplastic agents, specifically, dacarbazine, cis-platinum, tamoxifen and interferon-alfa. These reactions consisted of erythema, pruritus, and hypotension and occurred within hours of administration of chemotherapy. These events required medical intervention in some patients.

Myocardial injury, including myocardial infarction, myocarditis, ventricular hypokinesia, and severe rhabdomyolysis appear to be increased in patients receiving PROLEUKIN and interferon-alfa concurrently.

Exacerbation or the initial presentation of a number of autoimmune and inflammatory disorders has been observed following concurrent use of interferon-alfa and PROLEUKIN, including crescentic IgA glomerulonephritis, oculo-bulbar myasthenia gravis, inflammatory arthritis, thyroiditis, bullous pemphigoid, and Stevens-Johnson syndrome.

Although glucocorticoids have been shown to reduce PROLEUKIN-induced side effects including fever, renal insufficiency, hyperbilirubinemia, confusion, and dyspnea, concomitant administration of these agents with PROLEUKIN may reduce the antitumor effectiveness of PROLEUKIN and thus should be avoided.[12]

Beta-blockers and other antihypertensives may potentiate the hypotension seen with PROLEUKIN.

Delayed Adverse Reactions to Iodinated Contrast Media: A review of the literature revealed that 12.6% (range 11-28%) of 501 patients treated with various interleukin-2 containing regimens who were subsequently administered radiographic iodinated contrast media experienced acute, atypical adverse reactions. The onset of symptoms usually occurred within hours (most commonly 1 to 4 hours) following the administration of contrast media. These reactions include fever, chills, nausea, vomiting, pruritus, rash, diarrhea, hypotension, edema, and oliguria. Some clinicians have noted that these reactions resemble the immediate side effects caused by interleukin-2 administration, however the cause of contrast reactions after interleukin-2 therapy is unknown. Most events were reported to occur when contrast media was given within 4 weeks after the last dose of interleukin-2. These events were also reported to occur when contrast media was given several months after interleukin-2 treatment.[13]

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no studies conducted assessing the carcinogenic or mutagenic potential of PROLEUKIN.

There have been no studies conducted assessing the effect of PROLEUKIN on fertility. It is recommended that this drug not be administered to fertile persons of either gender not practicing effective contraception.

Pregnancy: *Pregnancy Category C.* PROLEUKIN has been shown to have embryolethal effects in rats when given in doses at 27 to 36 times the human dose (scaled by body weight). Significant maternal toxicities were observed in pregnant rats administered PROLEUKIN by IV injection at doses 2.1 to 36 times higher than the human dose during critical period of organogenesis. No evidence of teratogenicity was observed other than that attributed to maternal toxicity. There are no adequate well-controlled studies of PROLEUKIN in pregnant women. PROLEUKIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PROLEUKIN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children under 18 years of age have not been established.

Geriatric Use: There were a small number of patients aged 65 and over in clinical trials of PROLEUKIN; experience is limited to 27 patients, eight with metastatic melanoma and nineteen with metastatic renal cell carcinoma. The response rates were similar in patients 65 years and over as compared to those less than 65 years of age. The median number of courses and the median number of doses per course were similar between older and younger patients.

PROLEUKIN is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. The pattern of organ system toxicity and the proportion of patients with severe toxicities by organ system were generally similar in patients 65 and older and younger patients. There was a trend, however, towards an increased incidence of severe urogenital toxicities and dyspnea in the older patients.

ADVERSE REACTIONS

The rate of drug-related deaths in the 255 metastatic RCC patients who received single-agent PROLEUKIN® (aldesleukin) was 4% (11/255); the rate of drug-related deaths in the 270 metastatic melanoma patients who received single-agent PROLEUKIN was 2% (6/270).

The following data on common adverse events (reported in greater than 10% of patients, any grade), presented by body system, decreasing frequency and by preferred term (COSTART) are based on 525 patients (255 with renal cell cancer and 270 with metastatic melanoma) treated with the recommended infusion dosing regimen.

TABLE III: ADVERSE EVENTS OCCURRING IN ≥10% OF PATIENTS (n=525)

Body System	% Patients	Body System	% Patients
Body as a Whole		Metabolic and Nutritional Disorders	
Chills	52	Bilirubinemia	40
Fever	29	Creatinine increase	33
Malaise	27	Peripheral edema	28
Asthenia	23	SGOT increase	23
Infection	13	Weight gain	16
Pain	12	Edema	15
Abdominal pain	11	Acidosis	12
Abdomen enlarged	10	Hypomagnesemia	12
Cardiovascular		Hypocalcemia	11
Hypotension	71	Alkaline phosphatase increase	10
Tachycardia	23	Nervous	
Vasodilation	13	Confusion	34
Supraventricular tachycardia	12	Somnolence	22
Cardiovascular disorder[a]	11	Anxiety	12
Arrhythmia	10	Dizziness	11
Digestive		Respiratory	
Diarrhea	67	Dyspnea	43
Vomiting	50	Lung disorder[b]	24
Nausea	35	Respiratory disorder[c]	11
Stomatitis	22	Cough increase	11
Anorexia	20	Rhinitis	10
Nausea and vomiting	19	Skin and Appendages	
Hemic and Lymphatic		Rash	42
Thrombocytopenia	37	Pruritus	24
Anemia	29	Exfoliative dermatitis	18
Leukopenia	16	Urogenital	
		Oliguria	63

[a] Cardiovascular disorder: fluctuations in blood pressure, asymptomatic ECG changes, CHF.
[b] Lung disorder: physical findings associated with pulmonary congestion, rales, rhonchi.
[c] Respiratory disorder: ARDS, CXR infiltrates, unspecified pulmonary changes.

The following data on life-threatening adverse events (reported in greater than 1% of patients, grade 4), presented by body system, and by preferred term (COSTART) are based on 525 patients (255 with renal cell cancer and 270 with metastatic melanoma) treated with the recommended infusion dosing regimen.

TABLE IV: LIFE-THREATENING (GRADE 4) ADVERSE EVENTS (n= 525)

Body System	# (%) Patients	Body System	# (%) Patients
Body as a Whole		Metabolic and Nutritional Disorders	
Fever	5 (1%)	Bilirubinemia	13 (2%)
Infection	7 (1%)	Creatinine increase	5 (1%)
Sepsis	6 (1%)	SGOT increase	3 (1%)
Cardiovascular		Acidosis	4 (1%)
Hypotension	15 (3%)	Nervous	
Supraventricular tachycardia	3 (1%)	Confusion	5 (1%)
Cardiovascular disorder[a]	7 (1%)	Stupor	3 (1%)
Myocardial infarct	7 (1%)	Coma	8 (2%)
Ventricular tachycardia	5 (1%)	Psychosis	7 (1%)
Heart arrest	4 (1%)	Respiratory	
Digestive		Dyspnea	5 (1%)
Diarrhea	10 (2%)	Respiratory disorder[c]	14 (3%)
Vomiting	7 (1%)	Apnea	5 (1%)
Hemic and Lymphatic		Urogenital	
Thrombocytopenia	5 (1%)	Oliguria	33 (6%)
Coagulation disorder[b]	4 (1%)	Anuria	25 (5%)
		Acute kidney failure	3 (1%)

[a] Cardiovascular disorder: fluctuations in blood pressure.
[b] Coagulation disorder: intravascular coagulopathy.
[c] Respiratory disorder: ARDS, respiratory failure, intubation.

The following life-threatening (grade 4) events were reported by <1% of the 525 patients: hypothermia; shock; bradycardia; ventricular extrasystoles; myocardial ischemia; syncope; hemorrhage; atrial arrhythmia; phlebitis; AV block second degree; endocarditis; pericardial effusion; peripheral gangrene; thrombosis; coronary artery disorder; stomatitis; nausea and vomiting; liver function tests abnormal; gastrointestinal hemorrhage; hematemesis; bloody diarrhea; gastrointestinal disorder; intestinal perforation; pancreatitis; anemia; leukopenia; leukocytosis; hypocalcemia; alkaline phosphatase increase; BUN increase; hyperuricemia; NPN increase; respiratory acidosis; somnolence; agitation; neuropathy; paranoid reaction; convulsion; grand mal convulsion; delirium; asthma, lung edema; hyperventilation; hypoxia; hemoptysis; hypoventilation; pneumothorax; mydriasis; pupillary disorder; kidney function abnormal; kidney failure; acute tubular necrosis.

In an additional population of greater than 1,800 patients treated with PROLEUKIN-based regimens using a variety of doses and schedules (e.g., subcutaneous, continuous infusion, administration with LAK cells) the following serious adverse events were reported: duodenal ulceration; bowel necrosis; myocarditis; supraventricular tachycardia; permanent or transient blindness secondary to optic neuritis; transient ischemic attacks; meningitis; cerebral edema; pericarditis; allergic interstitial nephritis; tracheo-esophageal fistula.

In the same clinical population, the following fatal events each occurred with a frequency of <1%: malignant hyperthermia; cardiac arrest; myocardial infarction; pulmonary emboli; stroke; intestinal perforation; liver or renal failure; severe depression leading to suicide; pulmonary edema; respiratory arrest; respiratory failure. In patients with both metastatic RCC and metastatic melanoma, those with ECOG PS of 1 or higher had a higher treatment-related mortality and serious adverse events.

Most adverse reactions are self-limiting and, usually, but not invariably, reverse or improve within 2 or 3 days of discontinuation of therapy. Examples of adverse reactions with permanent sequelae include: myocardial infarction, bowel perforation/infarction, and gangrene.

In post-marketing experience, the following serious adverse events have been reported in a variety of treatment regimens that include interleukin-2: anaphylaxis; cellulitis; injection site necrosis; retroperitoneal hemorrhage; cardiomyopathy; cerebral hemorrhage; fatal endocarditis ; hypertension; cholecystitis; colitis; gastritis; hepatitis; hepatosplenomegaly; intestinal obstruction; hyperthyroidism; neutropenia; myopathy; myositis; rhabdomyolysis; cerebral lesions; encephalopathy; extrapyramidal syndrome; insomnia; neuralgia; neuritis; neuropathy (demyelination); urticaria; pneumonia (bacterial, fungal, viral).

Exacerbation or initial presentation of a number of autoimmune and inflammatory disorders have been reported (See "**WARNINGS**" section, "**PRECAUTIONS**" section, "**Drug Interactions**" subsection). Persistent but nonprogressive vitiligo has been observed in malignant melanoma patients treated with interleukin-2. Synergistic, additive and novel toxicities have been reported with PROLEUKIN used in combination with other drugs. Novel toxicities include delayed adverse reactions to iodinated contrast media and hypersensitivity reactions to antineoplastic agents (See "**PRECAUTIONS**" section, "**Drug Interactions**" subsection).

Experience has shown the following concomitant medications to be useful in the management of patients on PROLEUKIN therapy: a) standard antipyretic therapy, including nonsteroidal anti-inflammatories (NSAIDs), started immediately prior to PROLEUKIN to reduce fever. Renal function should be monitored as some NSAIDs may cause synergistic nephrotoxicity; b) meperidine used to control the rigors associated with fever; c) H_2 antagonists given for prophylaxis of gastrointestinal irritation and bleeding; d) antiemetics and antidiarrheals used as needed to treat other gastrointestinal side effects. Generally these medications were discontinued 12 hours after the last dose of PROLEUKIN.

Patients with indwelling central lines have a higher risk of infection with gram positive organisms.[3-11] A reduced incidence of staphylococcal infections in PROLEUKIN studies has been associated with the use of antibiotic prophylaxis which includes the use of oxacillin, nafcillin, ciprofloxacin, or vancomycin. Hydroxyzine or diphenhydramine has been used to control symptoms from pruritic rashes and continued until resolution of pruritus. Topical creams and ointments should be applied as needed for skin manifestations. Preparations containing a steroid (e.g., hydrocortisone) should be avoided. **NOTE: Prior to the use of any product mentioned, the physician should refer to the package insert for the respective product.**

OVERDOSAGE

Side effects following the use of PROLEUKIN® (aldesleukin) appear to be dose-related. Exceeding the recommended dose has been associated with a more rapid onset of expected dose-limiting toxicities. Symptoms which persist after cessation of PROLEUKIN should be monitored and treated supportively. Life-threatening toxicities may be ameliorated by the intravenous administration of dexamethasone, which may also result in loss of the therapeutic effects of PROLEUKIN.[12] **NOTE: Prior to the use of dexamethasone, the physician should refer to the package insert for this product.**

DOSAGE AND ADMINISTRATION

The recommended PROLEUKIN® (aldesleukin) for injection treatment regimen is administered by a 15-minute IV infusion every 8 hours. Before initiating treatment, carefully review the "**INDICATIONS AND USAGE**", "**CONTRAINDICATIONS**", "**WARNINGS**", "**PRECAUTIONS**", and "**ADVERSE REACTIONS**" sections, particularly regarding patient selection, possible serious adverse events, patient monitoring and withholding dosage. The following schedule has been used to treat adult patients with metastatic renal cell carcinoma (metastatic RCC) or metastatic melanoma. Each course of treatment consists of two 5-day treatment cycles separated by a rest period.

600,000 IU/kg (0.037 mg/kg) dose administered every 8 hours by a 15-minute IV infusion for a maximum of 14 doses. Following 9 days of rest, the schedule is repeated for another 14 doses, for a maximum of 28 doses per course, as tolerated. During clinical trials, doses were frequently withheld for toxicity (See "**Clinical Experience**" and "**Dose Modifications**" subsections). Metastatic RCC patients treated with this schedule received a median of 20 of the 28 doses during the first course of therapy. Metastatic melanoma patients received a median of 18 doses during the first course of therapy.

Retreatment: Patients should be evaluated for response approximately 4 weeks after completion of a course of therapy and again immediately prior to the scheduled start of the next treatment course. Additional courses of treatment should be given to patients only if there is some tumor shrinkage following the last course and retreatment is not contraindicated (See "**CONTRAINDICATIONS**" section). Each treatment course should be separated by a rest period of at least 7 weeks from the date of hospital discharge.

Dose Modifications: Dose modification for toxicity should be accomplished by withholding or interrupting a dose rather than reducing the dose to be given. Decisions to stop, hold, or restart PROLEUKIN therapy must be made after a global assessment of the patient. With this in mind, the following guidelines should be used:

Retreatment with PROLEUKIN is contraindicated in patients who have experienced the following toxicities:

Body System	
Cardiovascular	Sustained ventricular tachycardia (≥5 beats)
	Cardiac rhythm disturbances not controlled or unresponsive to management
	Chest pain with ECG changes, consistent with angina or myocardial infarction
	Cardiac tamponade
Respiratory	Intubation for >72 hours
Urogenital	Renal failure requiring dialysis >72 hours
Nervous	Coma or toxic psychosis lasting >48 hours
	Repetitive or difficult to control seizures
Digestive	Bowel ischemia/perforation
	GI bleeding requiring surgery

Doses should be held and restarted according to the following:

Body System	Hold dose for	Subsequent doses may be given if
Cardiovascular	Atrial fibrillation, supraventricular tachycardia, or bradycardia that requires treatment or is recurrent or persistent	Patient is asymptomatic with full recovery to normal sinus rhythm
	Systolic bp <90 mm Hg with increasing requirements for pressors	Systolic bp ≥90 mm Hg and stable or improving requirements for pressors
	Any ECG change consistent with MI, ischemia or myocarditis with or without chest pain; suspicion of cardiac ischemia	Patient is asymptomatic, MI and myocarditis have been ruled out, clinical suspicion of angina is low; there is no evidence of ventricular hypokinesia
Respiratory	O_2 saturation <90%	O_2 saturation >90%
Nervous	Mental status changes, including moderate confusion or agitation	Mental status changes completely resolved
Body as a Whole	Sepsis syndrome, patient is clinically unstable	Sepsis syndrome has resolved, patient is clinically stable, infection is under treatment
Urogenital	Serum creatinine >4.5 mg/dL or a serum creatinine of ≥4 mg/dL in the presence of severe volume overload, acidosis, or hyperkalemia	Serum creatinine <4 mg/dL and fluid and electrolyte status is stable
	Persistent oliguria, urine output of <10 mL/hour for 16 to 24 hours with rising serum creatinine	Urine output >10 mL/hour with a decrease of serum creatinine >1.5 mg/dL or normalization of serum creatinine
Digestive	Signs of hepatic failure including encephalopathy, increasing ascites, liver pain, hypoglycemia	All signs of hepatic failure have resolved*
	Stool guaiac repeatedly >3-4+	Stool guaiac negative
Skin	Bullous dermatitis or marked worsening of pre-existing skin condition, avoid topical steroid therapy	Resolution of all signs of bullous dermatitis

*Discontinue all further treatment for that course. A new course of treatment, if warranted, should be initiated no sooner than 7 weeks after cessation of adverse event and hospital discharge.

Reconstitution and Dilution Directions: Reconstitution and dilution procedures other than those recommended may alter the delivery and/or pharmacology of PROLEUKIN and thus should be avoided.

1. PROLEUKIN® (aldesleukin) is a sterile, white to off-white, preservative-free, lyophilized powder suitable for IV infusion upon reconstitution and dilution. **EACH VIAL CONTAINS 22 MILLION IU (1.3 MG) OF PROLEUKIN AND SHOULD BE RECONSTITUTED ASEPTICALLY WITH 1.2 ML OF STERILE WATER FOR INJECTION, USP. WHEN RECONSTITUTED AS DIRECTED, EACH ML CONTAINS 18 MILLION IU (1.1 MG) OF PROLEUKIN.** The resulting solution should be a clear, colorless to slightly yellow liquid. The vial is for single-use only and any unused portion should be discarded.
2. During reconstitution, the Sterile Water for Injection, USP should be directed at the side of the vial and the contents gently swirled to avoid excess foaming. DO NOT SHAKE.
3. The dose of PROLEUKIN, reconstituted with Sterile Water for Injection, USP (without preservative) should be diluted aseptically in 50 mL of 5% Dextrose Injection, USP (D5W) and infused over a 15-minute period.
   In cases where the total dose of PROLEUKIN is 1.5 mg or less (e.g., a patient with a body weight of less than 40 kilograms), the dose of PROLEUKIN should be diluted in a smaller volume of D5W. Concentrations of PROLEUKIN below 30 µg/mL and above 70 µg/mL have shown increased variability in drug delivery. Dilution and delivery of PROLEUKIN outside of this concentration range should be avoided.
4. Glass bottles and plastic (polyvinyl chloride) bags have been used in clinical trials with comparable results. It is recommended that plastic bags be used as the dilution container since experimental studies suggest that use of plastic containers results in more consistent drug delivery. **In-line filters should not be used when administering PROLEUKIN.**
5. Before and after reconstitution and dilution, store in a refrigerator at 2° to 8°C (36° to 46°F). Do not freeze. Administer PROLEUKIN within 48 hours of reconstitution. The solution should be brought to room temperature prior to infusion in the patient.
6. Reconstitution or dilution with Bacteriostatic Water for Injection, USP, or 0.9% Sodium Chloride Injection, USP should be avoided because of increased aggregation. PROLEUKIN should not be coadministered with other drugs in the same container.
7. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

PROLEUKIN® (aldesleukin) for injection is supplied in individually boxed single-use vials. Each vial contains 22 x 10^6 IU of PROLEUKIN. Discard unused portion.

NDC 53905-991-01 Individually boxed single-use vial

Store vials of lyophilized PROLEUKIN in a refrigerator at 2° to 8°C (36° to 46°F). PROTECT FROM LIGHT. Store in carton until time of use.

Reconstituted or diluted PROLEUKIN is stable for up to 48 hours at refrigerated and room temperatures, 2° to 25°C (36° to 77°F). However, since this product contains no preservative, the reconstituted and diluted solutions should be stored in the refrigerator.

Do not use beyond the expiration date printed on the vial. **NOTE:** This product contains no preservative.

Rx Only

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treatment.[7] Patients in both arms were followed until relapse, death, or 5 years post nephrectomy. The relapse rate was identical in both arms, 43%. In the radiotherapy group, 44% of patients developed significant complications to the stomach, duodenum, or liver and 19% of those radiation-related complications contributed to patient death.

The median survival time in the radiotherapy group was 26 months, compared to 62% survival at 26 months in the observation-only group. Although the difference in survival time was not statistically significant, researchers concluded that radiotherapy showed no beneficial effect on relapse rate or survival and produced an unacceptably high rate of complications.

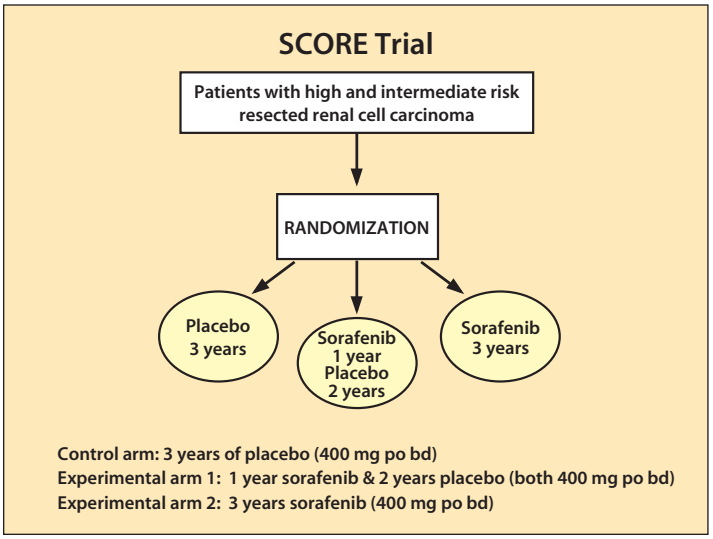
Adjuvant therapy with hormonal agents was also attempted in the 1980s. Agents such as medroxyprogesterone acetate (MPA) block glucocorticoid receptors on some renal tumor cells. Early studies with MPA showed a significant decrease in relapse rates compared to historical controls, which prompted a 5-year, prospective randomized study with 136 patients following radical nephrectomy and regional lymphadenectomy in Italy.[4]

Patients across five study centers received either 500 mg MPA three times weekly for one year or observation only for nonmetastatic renal cancer. After 5 years of follow-up, researchers found no correlation between sex steroid hormone receptors, relapses, and treatment. One third of patients in both arms relapsed after a median period of 17 months post nephrectomy. The median time was longer in the observation group (20 months) than in the treatment group (11 months), but the difference was not statistically significant. The disease-free survival rate at 5 years was 67.1% in the treatment group compared to 67.3% in the observation group.

In the treatment group, 56.9% of patients experienced complications that included loss of libido, significant weight gain, hypertension, hirsutism and amenorrhea in women, gluteal abscess, and diabetes. Treatment was discontinued in three additional patients because of hepatitis and retinal damage. Researchers concluded that MPA should not be used as adjuvant therapy

The next step was biologic adjuvant therapy, with trials stretching from the mid-1980s into the present. Therapy design was based on discoveries that tumor cells express cell surface antigens that can elicit immune responses specific to tumor types. The immune responses are mediated by CD8+ cytotoxic lymphocytes. The immune response can be amplified by cytokines produced by CD4+ helper cells, including IL-2 and interferon-gamma. Researchers suggested that immunizing patients against antigens derived from tumor cells, either alone or in combination with hormones, cytokines, immune adjuvants, or other agents could produce positive results.

Several groups tried active specific immunotherapy, a strategy that attempts to increase the patient's immune response to his or her specific tumor. One of the largest trials involved 120 patients randomized to observation only or treatment with irradiated autologous tumor cells plus bacillus Calmette-Guerin (BCG) following radical nephrectomy.[8] More than half of immunized patients developed delayed-type cutaneous hypersensitivity (DTCH) response to their own tumor cells but not to autologous normal renal cells. The observation-only group showed no DTCH response.



Sorafenib will be studied in a Phase 3 randomized, double-blind, controlled study comparing sorafenib with placebo in patients with resected primary RCC at high or intermediate risk of relapse. Patients will be randomized to one of three arms: placebo for 3 years, sorafenib (400 mg po bd) for 1 year and placebo for 2 years, or sorafenib (400 mg po bd) for 3 years.

After a median follow-up period of 61 months, the probability of 5-year disease-free survival was 63% for the treatment arm and 72% for the observation-only arm. That translates into a 5-year probability for overall survival of 69% for treated patients and 78% for controls. The difference in survival was not statistically significant.

The next attempt was interferon alfa following radical nephrectomy. Several studies have been published, none of them showing any statistically significant improvement in time to relapse or overall survival. One of the larger trials randomized 238 patients to observation or interferon alfa-NL.[5] Patients remained on treatment until recurrence, excessive toxicity, or cessation of treatment by patient or physician preference. There were no fatal toxicities in the treatment arm, but 11.4% of treated patients had grade 4 toxicities. Median survival was 7.4 years in the observation arm versus 5.1 years in the treatment arm. Time to recurrence was also longer in the observation arm, 3.0 years versus 2.2 years, but neither difference was statistically significant.

A high-dose IL-2 trial by the IL-2 Working Group in 69 patients was halted early because of a combination of expected toxicity and absence of benefit.[6] Researchers concluded that while high-dose bolus adjuvant therapy with IL-2 is feasible, it did not produce the clinically meaningful response need to offset its significant toxicity. IL-2 is typically administered in an inpatient setting with intensive care-level monitoring to deal with capillary leak syndrome. Supportive therapy usually requires low-dose vasopressors, antipyretics, and antinausea and antidiarrheal medications.

Current Approaches to Targeted Therapy

One of the first biologic successes was a randomized Phase 3

trial of an autologous renal tumor cell vaccine following radical nephrectomy.[9] A total of 558 patients at 55 institutions across Germany were randomized to treatment with an autologous renal tumor cell vaccine or observation. At 60 months and 70 months post surgery, the hazard ratios for tumor progression were 1.58 and 1.59 in favor of the vaccine group. Progression-free survival at 60 months and 70 months was 77.4% and 72% for the vaccine group compared to 67.8% and 59.3% for the control group.

The vaccine was well tolerated, but the positive results barely reached statistical significance. In addition, there were significant methodological questions raised almost immediately after the study was published. Questions included the number of patients lost following randomization (32%), the imbalance of the loss (99 from the vaccine group and 75 from the control group), and the lack of overall survival statistics presented by intention to treat. These statistics have now been presented and appear to confirm the benefit of this approach.

Heat Shock Proteins and an Autologous Vaccine

The vaccine approach continues to elicit interest. One of the most promising is Oncophage (vitespen, formerly HSPPC-96, Antigenics), based on heat shock protein technology. Heat shock proteins (HSPs) are ubiquitous molecules expressed by nearly all living organisms in response to heat and other stressors, including hypoxia, ischemia, hyperoxia, exposure to toxic radicals, and carcinogenesis.[10] The four primary HSPs, named for their molecular weight, are 27, 60, 70, and 90. They play a primary cytoprotective role following injury and promote cellular resistance to subsequent stresses. HSPs inhibit apoptosis, play a role in drug resistance, stimulate immune responses, and act as molecular chaperones, transporting and stabilizing proteins within the cell.

A wide range of tumor types, including RCC, has been shown to over-express HSPs. That suggests that HSPs may be used as a prognostic indicator as well as a target for treatment. HSPs associated with drug resistance may eventually be used to stratify tumors based on sensitivity to specific agents. HSPs can also increase tumor immunogenicity by triggering an immune response and stimulating destruction of tumor cells. So HSPs may act directly on tumor cells, be used as a target, or sensitize tumor cells to other treatments.

Oncophage is the first autologous HSP vaccine to move into Phase 3 trials. Vaccine is produced individually for each patient using a minimum of 7 grams of surgically resected tumor collected during nephrectomy. The tissue is frozen and shipped to a central facility for vaccine production. The finished product is designed for intradermal or subcutaneous injection, 25 mcg weekly for 4 weeks, then every other week until the individualized vaccine supply is exhausted.

In a Phase 2 study reported in 2003, 2 of 61 patients had partial remission of RCC, 1 had a complete remission and remained disease free for 2.5 years, and 18 had stable disease. Of 16 patients whose disease progressed, 7 became stable following the addition of IL-2 to the vaccine treatment. Median progression-free survival for the entire vaccine group was 18 weeks and 25 weeks for the vaccine plus IL-2 group. Two years after vaccination was begun, 30% of all patients were alive and there was no significant toxicity.

Phase 3 trials with more than 600 patients are currently under way at 145 sites worldwide to compare radical nephrectomy plus Oncophage with nephrectomy alone. Future trials will likely focus on increasing efficacy of HSP vaccines by the concomitant use of conventional cytotoxic, cytostatic, and biologic agents. Oncophage has been granted fast track designation by the Food and Drug Administration for use in RCC and metastatic melanoma.

Encouraging Results with Monoclonal Antibody WX-G250

A second approach is based on G250, a chimeric monoclonal antibody first produced in the 1980s by immunizing mice with human RCC homogenates.[11] G250 has since been found to be identical to carbonic anhydrase IX (CAIX), an antigen associated with a variety of tumor cells, including RCC. In normal cells, CAIX catalyzes the production of carbonic acid, which plays a role the regulation of pH within and around cells. CAIX over-expression appears to be mediated by hypoxia-inducible factor-alpha (HiF-alpha) and contributes to the acidic microenvironment that enhances tumor progression and metastasis.

The upregulation of HiF-alpha is common in von Hippel-Lindau gene mutations linked to clear cell RCC. Upregulation of HiF-alpha is also associated with the upregulation of vascular endothelial growth factor (VEGF), which promotes angiogenesis and tumor growth. While CAIX is overexpressed in many tumors, including cervical, uterine, breast, lung, esophageal, gastric, biliary tree, colorectal, bladder, skin, and kidney cancers, it is rarely expressed in normal tissues outside the gastrointestinal tract, gallbladder, and pancreatic ducts. CAIX is present on 95% of clear cell renal carcinomas but not on normal renal tissue.

The murine portion of G250 is immunogenic, inducing production of human antichimeric antibody (HACA). It is believed that the presence of HACA leads to rapid clearance, interfering with the biolocalization of renal cancer cells. The primary mechanism of action is antibody-dependent cellular cytotoxicity (ADCC), but other mechanisms of action may also be present.

Wilex AG, based in Munich, Germany, has completed Phase 1 and 2 trials with cG250 (WX-G250, now named Rencarex) following radical nephrectomy in progressive metastatic patients (stage IV). Phase 1 studies showed the agent to be safe and well tolerated both as monotherapy and in combination with IL-2 and interferon. In Phase 2 studies, 31% of patients showed clinical benefit, defined as either a response to treatment or stabilization of metastatic disease for at least 6 months. Two studies for which data are available show median survival times of 16 months and 22 months. A separate trial showed a 2-year survival rate of 41%. These figures are encouraging but cannot be definitive since they are compared with historical data.

In May 2004, Wilex launched ARISER (Adjuvant Rencarex Immunotherapy trial to Study Efficacy in non-metastatic Renal cell carcinoma) to evaluate WX-G250 ver-

sus placebo as adjuvant therapy. The international randomized trial will recruit 612 patients with nonmetastasized clear cell RCC at high risk of relapse following nephrectomy and lymphadenectomy. Patients will receive weekly treatment with either WX-G250 or placebo over 24 weeks. Patients will be followed at 3 months and 6 months, every 3 months during years 1 and 2, every 6 months during years 3 and 4, and annually during year 5 and thereafter.[12]

Approaching Approval: Sorafenib and Sunitinib

Vaccines are not the only new agents on the adjuvant scene. In 2005 encouraging data began to appear on two new products, sorafenib (Nexavar) and sunitinib (Sutent). Both drugs were well tolerated and both have shown significant activity against RCC. FDA approval of sorafenib was obtained in December 2005 and it is anticipated that sunitinib will obtain approval during 2006.

Sorafenib is an oral multikinase inhibitor that acts both on the tumor and its vasculature by targeting Raf kinase and receptor kinases VEGFR-2 (vascular endothelial growth factor receptor 2) and PDGFR-beta (platelet-derived growth factor receptor beta). Interim analysis of Phase 3 data reported at the 13th European Cancer Conference[13] showed a 39% improvement in survival for patients taking sorafenib versus placebo (hazard ratio .72, P=0.018). The preliminary results are based on 220 patient deaths that had occurred by May 31, 2005, and are promising, but not statistically significant at this time. A final survival analysis is planned when 540 deaths have occurred, which is not expected for some time.

Sorafenib will also be studied in a Phase 3 randomized, double-blind, controlled study comparing sorafenib with placebo in patients with resected primary RCC at high or intermediate risk of relapse (SORCE). SORCE will address the following questions:

- Does sorafenib for a mean of 2 years prolong survival?
- Does length of exposure to sorafenib correlate with survival?
- Which biological parameters predict benefit from sorafenib?
- Do the data corroborate with the Leibovich risk model?

To be eligible for SORCE, the following criteria must be met: no evidence of residual disease after resection of RCC; patients must have a Leibovich prognostic score of 3-8 (high or intermediate risk of metastatic RCC or death); no prior anticancer treatment other than nephrectomy; at least 4 weeks and no more than 3 months since surgery; any age but without a comorbidity expected to reduce life expectancy below 10 years from the time of trial entry; adequate bone marrow, renal, and hepatic function; and amylase less than 1.5 times the upper limit of normal. The primary end point will be metastasis-free survival. Patients will be randomized to one of three arms: placebo for 3 years, sorafenib (400 mg, po, bd) for 1 year and placebo for 2 years, or sorafenib (400 mg, po bd) for 3 years.

This 8-year study will address the key question of whether patients who most benefit from adjuvant sorafenib are those whose tumors display deregulated VEGF/PDGF signaling. In examining this issue, SORCE will help elucidate what has been proposed as a fundamental mechanism in the pathophysiology of RCC.

A multicenter Phase 2 trial of Sutent reported a total response rate of 40% as second-line therapy compared to the typical 15% response rate for standard treatment with high-dose IL-2 and interferon-alpha.[14] Sutent is an oral multitargeted tyrosine kinase inhibitor of PDGFR and VEGFR. In a trial with 63 patients, 40% had a partial response, 33% had stable disease, and 27% had progression. Of the 25 patients with a partial response, 6 had continuous response for longer than 12 months. In a second Phase 2 trial with 106 patients, both partial and complete responses were seen, but there was insufficient time to assess all responses. The Eastern Cooperative Oncology Group (ECOG) is planning a three-arm study comparing one year of sorafenib with one year of sunitinib with one year of placebo in patients who have had a T1B–T4 RCC resected.

Into the Future of Adjuvant Therapy

As new approaches and new therapies are being developed, it is vital to clarify which populations and individuals are at greatest risk and which are most likely to benefit from specific therapies. The TNM staging system remains the most widely used method, but researchers at the University of California at Los Angeles and other centers are working to improve prognosticative systems. Zisman's group at UCLA successfully integrated stage, grade, and ECOG performance status into a clinically useful tool to stratify RCC patients.[15]

The UCLA Integrated Staging System (UISS) combines a variety of useful and common variables, including TNM stage, Fuhrman grade, and ECOG-PS, plus the presence of metastatic or nonmetastatic disease. While UISS has provided improved diagnostic and prognostic information for RCC patients, future staging systems will include molecular biomarkers. UCLA researchers are working to integrate molecular data from tissue microarray assays into UISS to create a Molecular Integrated Staging System.[16]

Tissue samples from 381 patients, representing all stages of localized and metastatic RCC were stained for Ki-67, p53, gelsolin, CAIX, CAXII, PTEN, EpCAM, and vimentin. The markers were selected based on prior reports associating them with the development of malignancies. A prognostic model based on molecular markers had a high discriminating power, a statistically validated concordance index (C-index) of 0.75. A prognostic model based on a combination of clinical and molecular predictors had a C-index of 0.79. The combination model was more powerful than prognostic models based on grade alone (C = 0.65), TNM stage alone (C = 0.73), or UISS (C = 0.76).

One important aspect of all the current or planned adjuvant trials is to take steps to identify those patients who will most benefit from treatment. In this regard the molecular markers identified above might act both as prognostic and treatment selection markers.

Clinicians have already made significant progress from the days when patients needed up to 6 weeks to recover from open nephrectomy before undergoing adjuvant therapy. Patients who have undergone laparoscopic nephrectomy usually recover within a few days and are in a position to

NEW!
Simplified Inclusion Criteria

WILEX
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ARISER

Adjuvant **R**encarex® **I**mmunotherapy Phase **III** trial to **S**tudy **E**fficacy in non-metastatic **R**enal cell carcinoma

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Protocol ID:	WX-2003-07-HR
Purpose:	Evaluate efficacy (disease free survival and overall survival) and safety (incl. quality of life) of Rencarex® (WX-G250) versus placebo as adjuvant therapy for non-metastasized patients with clear cell RCC who are at high risk of recurrence after nephrectomy.
Patients:	Non-metastatic renal cell carcinoma at high risk of recurrence after nephrectomy
Drug:	Rencarex® (WX-G250)
Phase:	III
Study Design:	Randomized, double-blind, placebo-controlled

Eligibility: 18 years and older – both genders

Inclusion Criteria

- Primary clear cell renal cell carcinoma
- Prior nephrectomy
- Study entry not more than 8 weeks after nephrectomy
- No evidence of macroscopic and microscopic residual disease
- ECOG of 0
- Patients at high risk of recurrence (as defined in the study protocol)

Exclusion Criteria

- No patients with prior chemotherapy / immunotherapy / radiotherapy within the last 5 years
- No patients with pre-exposure to murine or chimeric antibody
- No patients with prior organ transplantation
- No history of prior malignancies within the last 5 years, except for surgically-cured non-melanoma skin cancer, or cervical carcinoma in situ
- No patients with any unrelated illness, which can significantly jeopardize patients' clinical status

More information: www.clinicaltrials.gov or www.cancer.gov/clinicaltrials, then search under: WX-2003-07-HR

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start adjuvant therapy protocols. Adding the expected impact of new biologic agents and new, more revealing staging systems incorporating molecular markers that can indicate preferential treatment choices will forever alter the practice and the expectations of adjuvant therapy for RCC.

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MEDICAL INTELLIGENCE (continued from page 3)

Mixed results on use of imatinib (Gleevec) in RCC

ROCHESTER, MINNESOTA—Mayo Clinic Cancer Center investigators report that imatinib mesylate (Gleevec), used to treat patients with gastrointestinal stromal cancers, is not likely to be effective for patients with high-grade renal cell carcinoma—the most aggressive kidney cancer. Results of the study were published in the January issue of *The Journal of Urology (See KCJ Journal Club)*.

PHILADELPHIA, PENNSYLVANIA—In a Phase 2 study of interferon-alpha plus either imatinib mesylate (Gleevec) or gefitinib (Iressa) in patients with metastatic renal cell carcinoma, interferon-alpha plus Iressa has turned out to be the safer and more effective combination. Lead investigator Robert J. Amato, DO, Director, Genitourinary Oncology Center, Methodist Hospital Research Institute, Houston, presented results at the International Conference on Molecular Targets and Cancer Therapeutics. To date, the researchers have treated 10 men and 2 women, median age of 51 years (range, 25-66 years). All have progressive metastatic renal cell carcinoma. Among the 8 patients treated with interferon/Iressa, 2 demonstrated a partial response, 1 a minor response, and 1 had stabilization of disease. In 4 subjects, it is too early to discern a response.

Moderate drinking may lower renal cell carcinoma risk

NEW YORK, NEW YORK—Moderate alcohol intake may be associated with a decreased risk of kidney cancer in middle-aged and older women, according to a study conducted in Sweden and published in the *International Journal of Cancer*. Dr Alicja Wolk, of the Karolinska Institute, Stockholm, and colleagues examined data on 59,237 women who were 40 to 76 years of age and cancer-free between 1987 and1990. A total of 132 cases of kidney cancer—specifically a common type called renal cell carcinoma—was diagnosed by 2004. Overall, the women who drank at least one serving of alcohol per week had a 38% lower risk of renal cell carcinoma than those who drank less. For women over 55 years old, the risk was reduced even more—by 66%. "The nature of the association between alcohol consumption and renal cell carcinoma is not well understood," Wolk and colleagues note.

Kidney Cancer Association Medical Advisory Board Expanded

EVANSTON, ILLINOIS—Eight members were recently added to the KCA's Medical Advisory Board that now includes 37 world-renowned physicians, scientists, and statisticians. Added to this distinguished panel were Jennifer Bacik, MS, Memorial Sloan-Kettering Cancer Center, New York; Prof P.H.M. De Mulder, MD, PhD University Medical CenterNijmegen, Norway; Timothy Eisen, MD, Royal Marsden Hospital, London; Bernard Escudier, MD, Institut Gustave-Roussy, Paris; Martin Gore, MD, Royal Marsden Hospital, London; Judith Manola, MS, Dana-Farber Cancer Institute, Boston; David Nanus, MD,Memorial Sloan-Kettering Cancer Center, New York; Sylvie Negrier, MD, Centre Leon Berard, Lyon, France;. Miah-Hiang Tay, MD, National Cancer Centre, Singapore; and David Nichol, MD, Princess Alexandra Hospital, Brisbane, Australia.

"We are grateful for the continued support of these experts," said Bill Bro, CEO of the KCA. "Their contribution of time and effort has resulted in unprecedented growth of our organization. We now reach nearly 72-thousand people in the U.S. and more than 100 other nations. These outstanding professionals have helped the KCA to become a truly international organization that serves people affected by renal cancers on a global scale."

 (continued from page 4)

sion. A durable clinical benefit was achieved in 8 of 35 patients (23%), including 3 with a partial response and 5 with stabilization at 24 weeks or greater. Mean survival was 22 months. In general treatment was well tolerated with little toxicity. The number of effector cells increased during treatment but lytic capacity per cell did not increase. ADCC and clinical outcome did not appear to correlate.

Conclusion: WX-G250 combined with low-dose interleukin-2 in patients with metastatic renal cell carcinoma is safe and well tolerated. With a substantial clinical benefit and a median survival of 22 months in patients with metastatic disease who have progressive disease at study entry combination therapy showed increased overall survival compared to WX-G250 monotherapy. Survival was at least similar to that of currently used cytokine regimens but with a favorable toxicity profile.

Vaccine-mediated antitumor immunity enhanced with T cell depletion

Dannull J, Su Z, Rizzieri D, et al. Enhancement of vaccine-mediated antitumor immunity in cancer patients after depletion of regulatory T cells. *J Clin Invest*. 2005;115:3623-3633.

Summary: This study investigated whether elimination of CD4/CD25 Tregs using the recombinant interleukin-2 diphtheria toxin conjugate DAB(389)IL-2 (also known as denileukin diftitox and ONTAK) is capable of enhancing the immunostimulatory efficacy of tumor RNA-transfected dendritic cell (DC) vaccines. DAB(389)IL-2 is capable of selectively eliminating CD25-expressing Tregs from the PBMCs of cancer patients without inducing toxicity on other cellular subsets with intermediate or low expression of CD25. DAB(389)IL-2-mediated Treg depletion resulted in enhanced stimulation of proliferative and cytotoxic T cell responses in vitro but only when DAB(389)IL-2 was omitted during T cell priming. DAB(389)IL-2 significantly reduced the number of Tregs present in the peripheral blood of metastatic renal cell carcinoma patients and abrogated Treg-mediated immunosuppressive activity in vivo. Moreover, DAB(389)IL-2-mediated elimination of Tregs followed by vaccination with RNA-transfected DCs significantly improved the stimulation of tumor-specific T cell responses when compared with vaccination alone.

Conclusion: The findings may have implications in the design of immune-based strategies that may incorporate the Treg depletion strategy to achieve potent antitumor immunity with therapeutic impact.

Celecoxib and IFN-alpha effects may be enhanced by immunostaining

Rini BI, Weinberg V, Dunlap S, et al. Maximal COX-2 immunostaining and clinical response to celecoxib and interferon alpha therapy in metastatic renal cell carcinoma. *Cancer*. 2005 [Epub ahead of print].

Summary: COX-2 is expressed in the majority of renal cell tumors and correlates with stage, grade, and microvessel density. On the basis of potential additive or synergistic antitumor effects, interferon-alpha and celecoxib, an oral COX-2 inhibitor, were given to patients with metastatic renal cell carcinoma in a Phase 2 trial. Patients with untreated, metastatic disease received interferon-alpha 3 million units daily and celecoxib 400 mg orally twice daily continuously until disease progression or unacceptable toxicity. Pretreatment, paraffin-embedded tumor samples were immunohistochemically stained for COX-2 expression and plasma basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) levels were assayed to determine predictive or prognostic potential. There were three partial responses among 25 patients treated (objective response rate, 12%). The observed median time to disease progression (TTP) for the entire cohort was 3.3 months. A significant association between maximal COX-2 staining and clinical response was observed: all patients who experienced an objective response demonstrated 3+ COX-2 tumor immunostaining (trend test: $P = .03$). Therapy was well tolerated without toxicity.

Conclusion: The addition of celecoxib to interferon-alpha did not increase the objective response rate or TTP of this unselected cohort. Maximal COX-2 tumor immunostaining may identify patents more likely to achieve clinical benefit with COX-2 inhibition in combination with interferon-alpha. Further investigation of this combination in 3+ COX-2-overexpressing renal cell tumors is warranted

Imatinib fails to show complete or partial responses in metastatic disease

Vuky J, Isacson C, Fotoohi M, et al. Phase II trial of imatinib (Gleevec®) in patients with metastatic renal cell carcinoma. *Invest New Drugs*. 2005 [Epub ahead of print].

Summary: Fourteen patients with metastatic renal cell carcinoma were treated on a Phase 2 trial with imatinib. Eligible patients had histologically confirmed renal cell carcinoma, metastatic and measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST), Karnofsky performance status (KPS) of at least 70%, life expectancy of more than 3 months, and adequate hematological, renal, and liver function. Imatinib was given orally at a dose of 400 mg bid. The most common toxicities were Grade II/III nausea (28%) and Grade II renal insufficiency (14%). All patients had tumor tested by immunohistochemistry (IHC) for KIT protein (CD117, DAKO). One tumor (7%) demonstrated strong, diffuse expression and the rest were negative.

Conclusion: No complete or partial responses were observed in 12 evaluable patients treated with imatinib.

EDITOR'S MEMO (continued from page 2)

this issue. Although the new molecules are attracting a lion's share of the attention, we need to remain mindful—and hopeful—regarding emerging strategies that could potentiate the use of immunotherapy as well. Ongoing studies are addressing these issues and we would be remiss if we did not examine new approaches to the use of cytokine-based therapy. Although they are still speculative, we may pause to consider the latest findings on targets like B7-H1 and the potential relevance for the use of immunotherapy.

We have already seen how the use of various scoring systems, including carbonic anhydrase IX as a prognostic marker, has significantly altered our perceptions of appropriate patient selection to maximize the use of high-dose interleukin-2 therapy. It is hoped that the use of B7-H1 could also emerge as an important marker, not only for prognosis but as a means of guiding patient selection. Although still speculative, the application of B7-H1 is a provocative and tantalizing prospect as we continue to revisit the role of interleukin-2 treatment.

Similarly, we expect to see new data emerging in the months ahead on the use of other biomarkers. In that sense, the Nexavar and Sutent announcements need to be viewed within the context of an expanding paradigm surrounding the diagnosis and treatment of renal cell carcinoma. All of the dots still need to be connected, but with each new milestone—and Nexavar and Sutent is one of them—we are delineating a clearer picture of the pathogenesis and treatment of this disease.

Robert A. Figlin, MD
Editor-in-Chief

GUEST EDITORIAL (continued from page 4)

the kidney cancer lobby is weakened when multiple organizations are contending for the limited attention and resources of legislators. "The bottom line is that kidney cancer is not a 'famous' disease," says Christopher Wood, MD, an associate professor of urology at the University of Texas M. D. Anderson Medical Center. "It doesn't affect the numbers that breast and prostate cancers do. Anything that is done to dilute or detract from the message that kidney cancer is an important malignancy worthy of research should be avoided."

Some disease advocates have begun lobbying the federal government to earmark funds specifically for kidney cancer. However, this approach is not only contrary to the KCA's position, it is also fundamentally at odds with the congressional directive for NIH funding, as stated in the Appropriations Committee's report accompanying their recommendations for FY2005:

> *The Committee reiterates its longstanding view that NIH should distribute funding on the basis of scientific opportunity. The Committee urges the Director and the Administration to continue to resist pressures to earmark, set aside and otherwise politicize these resources. . . . For example, there are no directives to fund particular research mechanisms, such as centers or requests for applications, or specific amounts of funding for particular diseases.*[2]

And the NIH, in turn, concurs with this recommendation:

> *From long experience, we know that research aimed at one target often hits another, e.g., a gene causing breast cancer in mice plays a role in the development of brain tissue. It is impossible to attribute research and discoveries like this to one disease.*[3]

Regardless of political necessity, the KCA agrees that broad-based medical funding is better for everyone. "We must remember that cancer research is not performed in a vacuum," says Bowen. "Research in one cancer area often leads to discoveries in another." A good example of this principle in action is the drug gemcitabine. First approved by the FDA for treatment of pancreatic cancer,[4] it has since shown promise in reducing the size of renal cell tumors.[5,6] By forming a unified front and working toward common goals, kidney cancer advocates can effect significant contributions in the fight for a cure that may ultimately benefit the entire cancer patient population.

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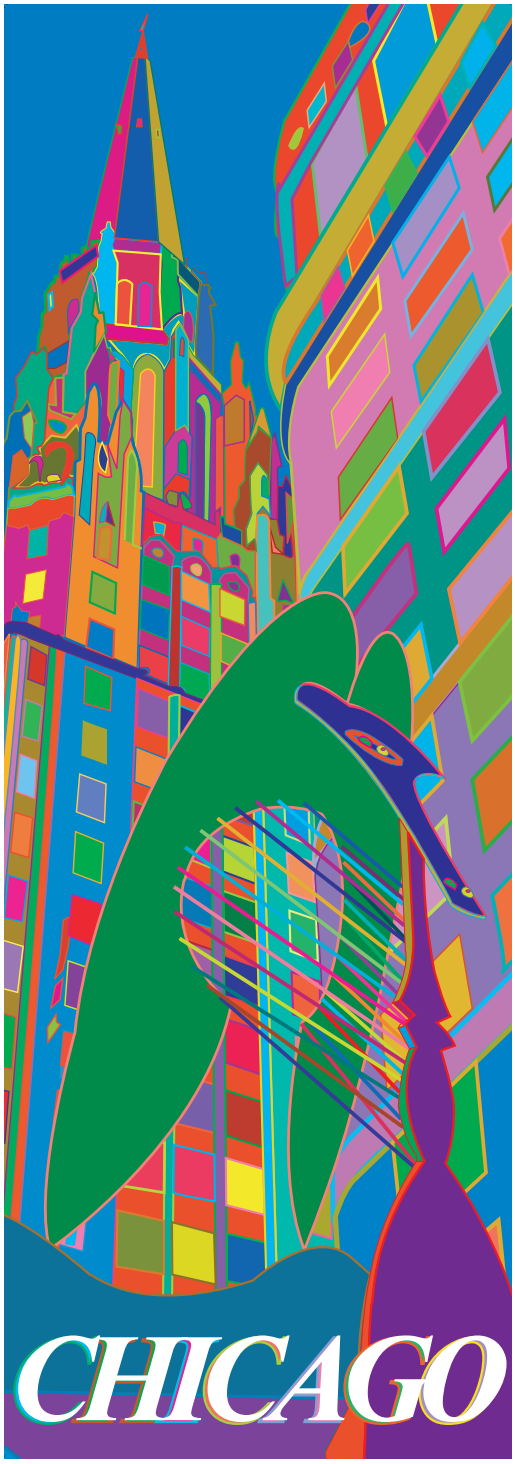

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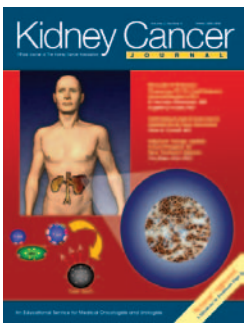

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Report Card on Adjuvant Therapy: Trials Build Enrollment, Enhancing Prospects for New Treatment Options
Tim Eisen, PhD, FRCP

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BRIEF SUMMARY
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INDICATIONS AND USAGE
NEXAVAR is indicated for the treatment of patients with advanced renal cell carcinoma.

CONTRAINDICATIONS
NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of NEXAVAR.

WARNINGS
Pregnancy Category D
In rats and rabbits, sorafenib has been shown to be teratogenic and to induce embryo-fetal toxicity (including increased post-implantation loss, resorptions, skeletal retardations, and retarded fetal weight). The effects occurred at doses considerably below the recommended human dose of 400 mg twice daily (approximately 500 mg/m^2/day on a body surface area basis). Adverse intrauterine development effects were seen at doses ≥1.2 mg/m^2/day in rats and 3.6 mg/m^2/day in rabbits (approximately 0.008 times the AUC seen in cancer patients at the recommended human dose). A NOAEL (no observed adverse effect level) was not defined for either species, since lower doses were not tested.

Based on the proposed mechanism of multikinase inhibition and multiple adverse effects seen in animals at exposure levels significantly below the clinical dose, sorafenib should be assumed to cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus (see **PRECAUTIONS – Information for Patients** section).

There are no adequate and well-controlled studies in pregnant women using NEXAVAR. Women of childbearing potential should be advised to avoid becoming pregnant while on NEXAVAR. NEXAVAR should be used during pregnancy only if the potential benefits justify the potential risks to the fetus (see **PRECAUTIONS – Information for Patients** section).

PRECAUTIONS
General
Dermatologic Toxicities: Hand-foot skin reaction and rash represent the most common adverse events attributed to NEXAVAR. Analysis of cumulative event rates from Study 1 suggest that rash and hand-foot skin reaction are usually CTCAE Grade 1 and 2 and generally appear during the first six weeks of treatment with NEXAVAR. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of NEXAVAR, or in severe or persistent cases, permanent discontinuation of NEXAVAR. Permanent discontinuation of therapy due to hand-foot skin reaction occurred in 3 of 451 NEXAVAR patients.

Hypertension: In Study 1, treatment-emergent hypertension was reported in approximately 16.9% of NEXAVAR-treated patients and 1.8% of patients in the placebo group. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was managed with standard antihypertensive therapy. Blood pressure should be monitored weekly during the first 6 weeks of NEXAVAR therapy and thereafter monitored and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, despite institution of antihypertensive therapy, temporary or permanent discontinuation of NEXAVAR should be considered. Permanent discontinuation due to hypertension occurred in 1 of 451 NEXAVAR patients.

Hemorrhage: An increased risk of bleeding may occur following NEXAVAR administration. In Study 1, bleeding regardless of causality was reported in 15.3% of patients in the NEXAVAR group and 8.2% of patients in the placebo group. The incidence of CTCAE Grade 3 and 4 bleeding events was 2% and 0%, respectively, in NEXAVAR patients, and 1.3% and 0.2%, respectively, in placebo patients. There was one fatal hemorrhage in each treatment group in Study 1. If any bleeding event necessitates medical intervention, permanent discontinuation of NEXAVAR should be considered.

Cardiac Ischemia and/or Infarction: In Study 1, the incidence of treatment-emergent cardiac ischemia/infarction events was higher in the NEXAVAR group (2.9%) compared with the placebo group (0.4%). Patients with unstable coronary artery disease or recent myocardial infarction were excluded from this study. Temporary or permanent discontinuation of NEXAVAR should be considered in patients who develop cardiac ischemia and/or infarction.

Race: Limited pharmacokinetic data on sorafenib 400 mg twice daily in a study in Japanese patients (n=6) showed a 45% lower systemic exposure (mean steady-state AUC) as compared to pooled Phase 1 pharmacokinetic data in Caucasian patients (n=25). The clinical significance of this finding is not known.

Warfarin Co-administration: Infrequent bleeding events or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on NEXAVAR therapy. Patients taking concomitant warfarin should be monitored regularly for changes in prothrombin time, INR or clinical bleeding episodes.

Wound Healing Complications: No formal studies of the effect of NEXAVAR on wound healing have been conducted. Temporary interruption of NEXAVAR therapy is recommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of NEXAVAR therapy following major surgical intervention. Therefore, the decision to resume NEXAVAR therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

Drug Interactions
Caution is recommended when administering NEXAVAR with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan) (see **CLINICAL PHARMACOLOGY – Drug-Drug Interactions** section).

Concomitant treatment with NEXAVAR resulted in a 21% increase in the AUC of doxorubicin. Caution is recommended when administering doxorubicin with NEXAVAR.

Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro* with K_i values of 6 and 1-2 μM, respectively. Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when co-administered with NEXAVAR. Caution is recommended when administering substrates of CYP2B6 and CYP2C8 with NEXAVAR.

Patients with Hepatic Impairment
In vitro and *in vivo* data indicate that sorafenib is primarily metabolized by the liver. Systemic exposure and safety data were comparable in patients with Child-Pugh A and B hepatic impairment. NEXAVAR has not been studied in patients with Child-Pugh C hepatic impairment. No dose adjustment is necessary when administering NEXAVAR to patients with Child-Pugh A and B hepatic impairment (see **CLINICAL PHARMACOLOGY – Hepatic Impairment** section).

Patients with Renal Impairment
NEXAVAR has not been studied in patients with severe renal impairment (CrCl <30 mL/min) or in patients undergoing dialysis.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been performed with sorafenib.

Sorafenib was clastogenic when tested in an *in vitro* mammalian cell assay (Chinese Hamster Ovary) in the presence of metabolic activation. Sorafenib was not mutagenic in the *in vitro* Ames bacterial cell assay or clastogenic in an *in vivo* mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (<0.15%), was positive for mutagenesis in an *in vitro* bacterial cell assay (Ames test) when tested independently.

No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. However, results from the repeat-dose toxicity studies suggest there is a potential for sorafenib to impair reproductive performance and fertility. Multiple adverse effects were observed in male and female reproductive organs, with the rat being more susceptible than mice or dogs. Typical changes in rats consisted of testicular atrophy or degeneration, degeneration of epididymis, prostate, and seminal vesicles, central necrosis of the corpora lutea and arrested follicular development. Sorafenib-related effects on the reproductive organs of rats were manifested at daily oral doses ≥30 mg/m^2 (approximately 0.5 times the AUC in cancer patients at the recommended human dose). Dogs showed tubular degeneration in the testes at 600 mg/m^2/day (approximately 0.3 times the AUC at the recommended human dose) and oligospermia at 1200 mg/m^2/day of sorafenib.

Adequate contraception should be used during therapy and for at least 2 weeks after completing therapy.

Pregnancy Category D
(see **WARNINGS**)

Nursing Mothers
It is not known whether sorafenib is excreted in human milk. Following administration of ^{14}C-sorafenib to lactating Wistar rats, approximately 27% of the radioactivity was secreted into the milk. The milk to plasma AUC ratio was approximately 5:1.

Because many drugs are excreted in human milk and because the effects of sorafenib on infants have not been studied, women should be advised against breast-feeding while receiving NEXAVAR.

Pediatric Use
The safety and effectiveness of NEXAVAR in pediatric patients have not been studied.

Repeat dosing of sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at daily sorafenib doses ≥600 mg/m^2 (approximately 0.3 times the AUC at the recommended human dose), hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m^2/day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the dentin composition at 600 mg/m^2/day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

Geriatric Use
In total, 32% of RCC patients treated with NEXAVAR were age 65 years or older, and 4% were 75 and older. No differences in safety or efficacy were observed between older and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Information for Patients (see **Patient Information About: NEXAVAR**)
Physicians should inform female patients that NEXAVAR may cause birth defects or fetal loss and that they should not become pregnant during treatment with NEXAVAR and for at least 2 weeks after stopping treatment. Both male and female patients should be counseled to use effective birth control during treatment with NEXAVAR and for at least 2 weeks after stopping treatment. Female patients should also be advised against breast-feeding while receiving NEXAVAR.

Patients should be advised of the possible occurrence of hand-foot skin reaction and rash during NEXAVAR treatment and appropriate countermeasures. Patients should be informed that hypertension may develop during NEXAVAR treatment, especially during the first six weeks of therapy, and that blood pressure should be monitored regularly during treatment.

Physicians should inform patients that NEXAVAR may increase the risk of bleeding and that they should promptly report any episodes of bleeding.

Physicians should also discuss with patients that cardiac ischemia and/or infarction has been reported during NEXAVAR treatment, and that they should immediately report any episodes of chest pain or other symptoms of cardiac ischemia and/or infarction.

ADVERSE REACTIONS
Safety evaluation of NEXAVAR is based on 1286 cancer patients who received NEXAVAR as monotherapy and 165 patients who received NEXAVAR concurrently with chemotherapy. A total of 346 patients were exposed to NEXAVAR monotherapy for greater than 6 months. A total of 664 RCC patients received NEXAVAR monotherapy, of whom 215 were treated for at least 6 months.

Table 2 shows the percent of patients experiencing treatment-emergent adverse events that were reported in at least 10% of patients who received NEXAVAR in a Phase 3, international, multicenter, randomized, double blind, placebo-controlled trial in patients with advanced renal cell carcinoma who had received one prior systemic therapy. CTCAE Grade 3 treatment-emergent adverse events were reported in 31% of patients receiving NEXAVAR compared to 22% of patients receiving placebo. CTCAE Grade 4 treatment-emergent adverse events were reported in 7% of patients receiving NEXAVAR compared to 6% of patients receiving placebo.

Table 2: Treatment-Emergent Adverse Events Reported in at Least 10% of NEXAVAR-Treated Patients – Phase 3 Study

Adverse Event NCI-CTCAE v3 Category/Term	NEXAVAR N=451			Placebo N=451		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Event	95	31	7	86	22	6
Cardiovascular, General						
Hypertension	17	3	<1	2	<1	0
Constitutional symptoms						
Fatigue	37	5	<1	28	3	<1
Weight loss	10	<1	0	6	0	0
Dermatology/skin						
Rash/desquamation	40	<1	0	16	<1	0
Hand-foot skin reaction	30	6	0	7	0	0
Alopecia	27	<1	0	3	0	0
Pruritus	19	<1	0	6	0	0
Dry skin	11	0	0	4	0	0
Gastrointestinal symptoms						
Diarrhea	43	2	0	13	<1	0
Nausea	23	<1	0	19	<1	0
Anorexia	16	<1	0	13	1	0
Vomiting	16	<1	0	12	1	0
Constipation	15	<1	0	11	<1	0
Hemorrhage/bleeding						
Hemorrhage – all sites	15	2	0	8	1	<1
Neurology						
Neuropathy-sensory	13	<1	0	6	<1	0
Pain						
Pain, abdomen	11	2	0	9	2	0
Pain, joint	10	2	0	6	<1	0
Pain, headache	10	<1	0	6	<1	0
Pulmonary						
Dyspnea	14	3	<1	12	2	<1
Cough	13	<1	0	14	<1	0

The rate of adverse events (including events associated with progressive disease) resulting in permanent discontinuation was similar in both the NEXAVAR and placebo groups (10% of NEXAVAR patients and 8% of placebo patients).

Safety was also assessed in a Phase 2 study pool comprised of 638 NEXAVAR-treated patients, including 202 patients with RCC, 137 patients with hepatocellular carcinoma, and 299 patients with other cancers. The most common drug-related adverse events reported in NEXAVAR-treated patients in this pool were rash (38%), diarrhea (37%), hand-foot skin reaction (35%), and fatigue (33%). The respective rates of CTC (v 2.0) Grade 3 and 4 drug-related adverse events in NEXAVAR-treated patients were 37% and 3%, respectively.

Additional Data from Multiple Clinical Trials
The following additional drug-related adverse events and laboratory abnormalities were reported from clinical trials of NEXAVAR in 1286 cancer patients who received NEXAVAR as monotherapy (*very common* 10% or greater, *common* 1 to less than 10%, *uncommon* 0.1% to less than 1%):

Cardiovascular: *Uncommon:* hypertensive crisis, myocardial ischemia and/or infarction

Dermatologic: *Very common:* erythema *Common:* exfoliative dermatitis, acne, flushing *Uncommon:* folliculitis, eczema, erythema multiforme

Digestive: *Very common:* increased lipase, increased amylase *Common:* mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia *Uncommon:* pancreatitis, gastrointestinal reflux, gastritis

Note that elevations in lipase are very common (41%, see below); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values

General Disorders: *Very common:* asthenia, pain (including mouth pain, bone pain, and muscle pain) *Common:* decreased appetite, influenza-like illness, pyrexia *Uncommon:* infection

Hematologic: *Very common:* leukopenia, lymphopenia *Common:* anemia, neutropenia, thrombocytopenia *Uncommon:* INR abnormal

Hypersensitivity: *Uncommon:* hypersensitivity reactions (including skin reactions and urticaria)

Metabolic and Nutritional: *Very common:* hypophosphatemia *Common:* transient increases in transaminases *Uncommon:* dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism

Musculoskeletal: *Common:* arthralgia, myalgia

Nervous System and Psychiatric: *Common:* depression *Uncommon:* tinnitus

Reproductive: *Common:* erectile dysfunction *Uncommon:* gynecomastia

Respiratory: *Common:* hoarseness *Uncommon:* rhinorrhea

In addition, the following medically significant adverse events were reported infrequently during clinical trials of NEXAVAR: cerebral hemorrhage, transient ischemic attack, cardiac failure, arrhythmia, thromboembolism, acute renal failure. For these events, the causal relationship to NEXAVAR has not been established.

℞ Only

For more information call 1-866-NEXAVAR (1-866-639-2827) or visit www.nexavar.com

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References:
1. Escudier B, Szczylik C, Eisen T, et al. Randomized phase III trial of the multi-kinase inhibitor sorafenib (BAY 43-9006) in patients with advanced RCC. Paper presented at: ECCO 13—the European Cancer Conference; November 3, 2005; Paris, France. **2.** Data on file, Bayer Pharmaceuticals Corporation, 2006.

INTRODUCING THE FIRST MULTI-KINASE INHIBITOR
FOR ADVANCED RENAL CELL CARCINOMA (RCC)

Proven results from the largest Phase 3 study in ADVANCED RCC

INTRODUCING THE FIRST MULTI-KIN

Target Efficacy

Important Safety Considerations

Hypertension may occur early in the course of Nexavar therapy and blood pressure should be monitored weekly during the first 6 weeks of therapy and treated as needed.

Incidence of bleeding regardless of causality was 15% for Nexavar vs 8% for placebo patients and the incidence of treatment-emergent cardiac ischemia/infarction was 2.9% for Nexavar vs 0.4% for placebo.

Dermatologic toxicities (rash/desquamation and hand-foot skin reaction) represent the most common adverse events. Other common treatment-emergent adverse events were diarrhea, fatigue, alopecia, and nausea/vomiting. Grade 3/4 adverse events were 38% for Nexavar vs 28% for placebo.

Women of child-bearing potential should be advised to avoid becoming pregnant and advised against breast-feeding.

Elevations in serum lipase and reductions in serum phosphate of unknown etiology have been associated with Nexavar. When administering Nexavar with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (eg, irinotecan), doxorubicin, and substrates of CYP2B6 and CYP2C8, caution is recommended.

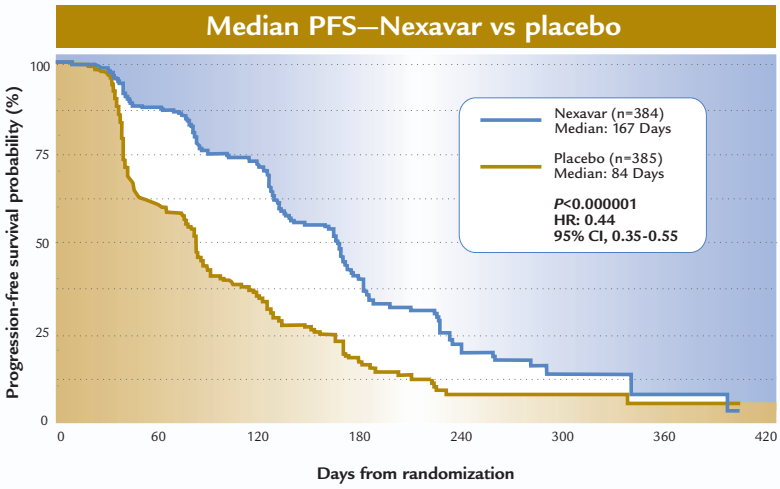
In cases of any severe or persistent side effects, temporary treatment interruption, dose modification, or permanent discontinuation of Nexavar should be considered.

Nexavar is indicated for the treatment of patients with Advanced Renal Cell Carcinoma.
Please see brief summary of Prescribing Information on following page.

ASE INHIBITOR FOR ADVANCED RCC

Focus on Life

New Oral Nexavar doubled median progression-free survival (PFS) to 6 months vs 3 months with placebo (*P*<0.000001; HR: 0.44; 95% CI, 0.35-0.55)[1]



Overall survival was longer for Nexavar than placebo

- Planned interim survival analysis based on 220 deaths, with a hazard ratio of 0.72 (95% CI, 0.55-0.95)[2]
- Nexavar-treated patients had a 28% reduction in risk of mortality relative to placebo-treated patients
- The analysis did not meet the prespecified criteria for statistical significance
- Additional analyses are planned as survival data mature

Generally well tolerated

- Discontinuations due to adverse events were comparable: Nexavar 10% vs placebo 8%
- The incidence of Grade 3/4 myelosuppression comparable to placebo (neutropenia was 5% Nexavar vs 2% placebo, thrombocytopenia was 1% Nexavar vs 0% placebo)

New Oral Nexavar® (sorafenib) tablets

www.NEXAVAR.com

THE BALANCED APPROACH

In the Next Issue of *Kidney Cancer Journal*
Prior to the 2006 ASCO Meeting

A full report on the Renal Cell Carcinoma Sessions of the
5th Multi-Disciplinary Symposium on Genitourinary Cancers

Featuring:

- Important data from leading investigators derived from interactive case-based lectures on surgical management, including localized disease management
- Role of debulking nephrectomy in metastatic disease
- Systemic therapy
- Initial standard of care for metastatic RCC: cytokines vs VEGF-targeted therapy
- Molecular predictors of response to VEGF-targeted agents in RCC
- Tissue-based analysis of VEGF-targeted therapy
- IL-2 response and CA9 expression
- Molecular and immunohistochemical data
- Chairman: Nicholas J. Vogelzang, MD, Director, Nevada Cancer Institute, Las Vegas, Nevada

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