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

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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 \( \geq 3 \) months. Median time to progression in the 63 patients was 8.7 months.

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 contact the Patient Advocate Foundation at www.patientadvocate.org. The Kidney Cancer Association (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.
New data support study of mTOR inhibitors
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
Summary: WX-G250 is a chimeric monoclonal antibody that binds to carbonic anhydrase IX (cicaG250/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 progression.
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GUEST EDITORIAL
Divided We Fall: How Competition Can Compromise the Cause

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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), but
(continued on page 24)
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. 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. Evidence is building for a strong connection between B7-H1 and a number of solid human malignancies, 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
- Induced B7-H1 expression on activated T cells impairs both T-cell function and survival, and expression of B7-H1 on myeloid dendritic cells associated with ovarian carcinoma has been found to suppress T-cell activation
- 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

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.
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. 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. 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. 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. 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 ≤ .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. 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. 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. 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. 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.

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. 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
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 observations13,13 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 stimulates 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 al15 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.

**References**

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 interleukin-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 coregulatory 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.
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.

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

Survival rates of 35% to 50%.\textsuperscript{5} This retrospective analysis of long-term survival, Kavolius et al documented a 5-year metastases from renal cell carcinoma and a further analysis further study is needed to identify which patients would be the best candidates for this technique and as an alternative to surgery.\textsuperscript{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.

\textbf{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%. 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. 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. 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. 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.

References

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 United States and 12,660 deaths. Although the diagnosis of RCC is increasing at about 1.5% annually, survival rates have not changed significantly in decades.

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. Trials with some hormonal agents and cytokine agents 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. 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.

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.

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
Stage IV patients can achieve long-term durable remissions

6.7+ years
(Median duration of complete response in METASTATIC RENAL CELL CARCINOMA)

4.9+ years
(Median duration of complete response in METASTATIC MELANOMA)

For a partial reference list of physicians and institutions experienced in the administration of PROLEUKIN® therapy, please visit www.proleukin.com/referral.

IMPORTANT SAFETY INFORMATION

Therapy with PROLEUKIN® (aldesleukin) for injection should be restricted to patients with normal cardiac and pulmonary functions as defined by thallium stress testing and formal pulmonary function testing. Extreme caution should be used in patients with a normal thallium stress test and a normal pulmonary function test who have a history of cardiac or pulmonary disease.

PROLEUKIN® should be administered in a hospital setting under the supervision of a qualified physician experienced in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.

PROLEUKIN® administration has been associated with capillary leak syndrome (CLS), which is characterized by a loss of vascular tone, and extravasation of plasma proteins and fluid into the extravascular space. CLS results in hypotension and reduced organ perfusion, which may be severe and can result in death. CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.

PROLEUKIN® treatment is associated with impaired neutrophil function (reduced chemotaxis), and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Consequently, preexisting bacterial infections should be adequately treated prior to initiation of PROLEUKIN® therapy. Patients with indwelling central lines are particularly at risk for infection with gram positive microorganisms. Antibiotic prophylaxis with oxacillin, nafcillin, ciprofloxacin, or vancomycin has been associated with a reduced incidence of staphylococcal infections.

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.
DESCRIPTION
Proleukin (aldesleukin) is a recombinant human interferon-α2b product, is a high-purity protein with a molecular weight of approximately 16,500 Daltons. The chemical nature of the protein is identical to that of the natural interferon-α2b. It is produced by recombinant DNA technology using a genetically engineered Escherichia coli strain containing an interferon-α2b gene, using genetic engineering techniques that have not modiﬁed the E. coli-2-k.1, and the resulting expression clone encodes a mature human interferon-α2b. This recombinant interferon-α2b is derived from strains selected for enhanced interferon production and for resistance to production-limiting recombinant bacterial cell toxins, by enhancement of plasmid stability. It is a mixture of the interferon forms α2b, containing α2b, α2a, and γ interferons. The production process for Proleukin involves fermentation in a continuous medium containing synthetic nutrients, with the antiviral activity of the product not being determined by the antiviral activity of the fermentation by-product. 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 circulatory system by both glomerular filtration and peritubular extraction in the kidney.5-8 This dual mechanism for delivery of Proleukin to the proximal tubule may account for the preserved function of the kidney in the treatment of patients with end-stage renal disease.

CLINICAL PHARMACOLOGY
Proleukin (aldesleukin) has been shown to possess the biological activities of human recombinant interferon-α2b. In vitro studies of Proleukin therapy: Patients treated with Proleukin show the expected clinical response of a typical interferon-α therapy, including suppression of viral replication, activation of cytotoxic T lymphocytes, enhancement of cellular immune function and induction of interferon production. The in vivo administration of Proleukin in animals and humans produces minimal immunological effects in a dose-dependent manner. These effects include activation of cellular immunity with profound lymphocytosis, eosinophilia, and thrombocytopenia, cytokine production, respiratory irritant requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.

Proleukin treatment is associated with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection, including skin and bacterial endocarditis. Consequently, primary bacterial infections should be sought and treated before Proleukin therapy is initiated. In patients with bilateral interstitial lung disease, particular care is needed in this regard. In patients with severe or chronic illness, secondary infections can be a major clinical problem. In patients with advanced malignant disease, neutrophil dysfunction is extremely common. In such patients, secondary infections are an important cause of mortality. The mortality rate for such patients is higher in those receiving Proleukin than in patients with comparable disease who receive other forms of therapy.

Some patients may experience anemia, neutropenia, leukopenia, or thrombocytopenia, as well as eosinophilia, which is characterized by a loss of vascular tone and extravasation of plasma proteins. Plasma protein extravasation and tissue edema result from impaired lymphatics and hyaluronidase function which may be severe and can result in death. CSL is associated with a significant risk of adverse reactions which are dose-related and progressive. Adverse reactions include hypotension, episodic, or sustained hypertension, bradycardia, tachycardia, chest pain, diarrhea; and ventricular arrhythmias. Prophylactic use of angiotensin-converting enzyme inhibitors may be useful. In addition to the cardiovascular events, adenocarcinoma of the lung, gastrointestinal hemorrhage, and bilateral interstitial lung disease are known complications of Proleukin therapy in animals and humans.

Pharmacokinetics
Proleukin (aldesleukin) is a biologically active non-covalent bi-aryl and bi-aromatic conjugate with a weight average of 27 percent recombinant protein. The half-life of Proleukin is prolonged, and its metabolic clearance is decreased when compared to natural interferon-α2b. The elimination of Proleukin from the body by metabolism in the kidneys and by bile with or without exposure to the renal tubular epithelium is similar to the elimination of Proleukin in the rat; 65-70% of the dose is recovered in the urine and 35-40% is recovered in the feces. The major metabolite is Proleukin-α2b, as determined by radioimmunoassay of Proleukin fractions in the rat. It has been estimated that approximately 10% of the administered dose is excreted in the urine. Final metabolism and excretion of Proleukin occurs via renal excretion of inactive metabolites. 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 circulatory system by both glomerular filtration and peritubular extraction in the kidney.5-8 This dual mechanism for delivery of Proleukin to the proximal tubule may account for the preserved function of the kidney in the treatment of patients with end-stage renal disease.

Modifications
Proleukin (aldesleukin) is contraindicated in patients with a known history of hyperчувствительность to 2- or any component of the Proleukin formulation. Proleukin is contraindicated in patients with a history of hyperчувствительность to the use of biologic response modifiers, including recombinant cytokines. Proleukin is contraindicated in patients with a history of a significant cardiovascular event, including myocardial infarction, unstable angina, or congestive heart failure, or who are at risk for such events, such as patients with heart failure or hypertension. Proleukin is contraindicated in patients with a history of bilateral interstitial lung disease, including pulmonary fibrosis. Proleukin is contraindicated in patients with a history of hypothyroidism, including hypothyroidism due to radiation therapy or surgery. Proleukin is contraindicated in patients with a history of hyperчувствительность to Proleukin. Proleukin is contraindicated in patients with a history of severe hepatic impairment, including cirrhosis. Proleukin is contraindicated in patients with a history of severe renal impairment, including dialysis-dependent renal failure. Proleukin is contraindicated in patients with a history of hematopoietic malignancy, including leukemia and lymphoma. Proleukin is contraindicated in patients with a history of autoimmune disease, including rheumatoid arthritis and lupus. Proleukin is contraindicated in patients with a history of hemolytic anemia, including hemolytic anemia due to hereditary spherocytosis or sickle cell disease. Proleukin is contraindicated in patients with a history of chronic kidney disease, including chronic kidney disease due to nephrotic syndrome or lupus nephritis. Proleukin is contraindicated in patients with a history of chronic liver disease, including chronic liver disease due to primary biliary cirrhosis or alcoholic hepatitis. Proleukin is contraindicated in patients with a history of prior exposure to Proleukin products. Proleukin is contraindicated in patients with a history of uncontrolled diabetes mellitus, including diabetes mellitus type I or II. Proleukin is contraindicated in patients with a history of uncontrolled hypertension, including hypertension due to secondary causes. Proleukin is contraindicated in patients with a history of uncontrolled hypothyroidism, including hypothyroidism due to primary causes.

WARNINGS
Because of the severe adverse events which generally accompany Proleukin (aldesleukin) therapy, close monitoring is required to identify patients with significant cardiac, pulmonary, renal, hepatic, or CNS dysfunction prior to treatment with Proleukin. Proleukin is contraindicated in patients with a history of bilateral interstitial lung disease, including pulmonary fibrosis, pulmonary hypertension, and CNS dysfunction who may experience adverse events, including cardiac and pulmonary events, during Proleukin therapy. Patients with a history of myocardial infarction or unstable angina should not be treated with Proleukin. Patients with a history of congestive heart failure should not be treated with Proleukin. Patients with a history of chronic kidney disease, including chronic kidney disease due to nephrotic syndrome or lupus nephritis, should not be treated with Proleukin. Patients with a history of chronic liver disease, including chronic liver disease due to primary biliary cirrhosis or alcoholic hepatitis, should not be treated with Proleukin. Patients with a history of uncontrolled diabetes mellitus, including diabetes mellitus type I or II, should not be treated with Proleukin. Patients with a history of uncontrolled hypertension, including hypertension due to secondary causes, should not be treated with Proleukin. Patients with a history of uncontrolled hypothyroidism, including hypothyroidism due to primary causes, should not be treated with Proleukin.

ADVERSE REACTIONS
Serious adverse events that generally accompany Proleukin (aldesleukin) therapy include life-threatening and fatal events. Life-threatening or fatal events include hypotension, cardiac arrhythmias, pulmonary edema, pericardial effusion, and pulmonary hemorrhage. The incidence of life-threatening or fatal events is increased in patients with advanced renal or liver disease, and in patients with a history of malignancy. The most common serious adverse events that generally accompany Proleukin (aldesleukin) therapy include life-threatening or fatal events.

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Metabolic and Nutritional Disorders

Dose-related deaths in the 255 metastatic RCC patients who received single-agent PROLEUKIN® (aldesleukin) was 4% (10). The rate of drug-related deaths in the 255 metastatic RCC patients who received single-agent PROLEUKIN® was 2% (6). The following adverse events occurred in greater than 10% of patients, any grade:

- GI bleeding requiring surgery
- Nausea and vomiting
- Anorexia
- Rhinitis
- Hypomagnesemia
- Fever
- Weight gain

In the same clinical population, the following fatal events each occurred with a frequency of 1% or more:

- Cardiac arrest
- Respiratory failure
- Wound sepsis
- Wound dehiscence
- Peritonitis

In an additional population of greater than 1,800 patients treated with PROLEUKIN®-based regimens, the following adverse events have been reported with a frequency of 1% or more:

- Cardiac ischemia
- Sepsis

For additional information, contact Chiron Therapeutics Professional Services 1-800-331-4361. © 2000 Chiron Corporation U.S. License No. 1106 4,853,332; 4,959,314; 5,464,939 4,104,683; 4,106,542; 4,804,826; 4,853,332; 4,959,314; 5,464,939

References

1. Doyle MV, Lee MT, Fong S. Comparison of the biological activities of human recom-

2. Glass bottles and plastic (polyvinyl chloride) bags have been used in clinical trials with PROLEUKIN®. Each vial contains 22 x 106 IU of PROLEUKIN. Discard unused portion.

CONTRAINDICATIONS

- Severe immunologic disease
- Severe autoimmune disease
- Apparently normal person

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treatment. 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.

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
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 in 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.

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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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 prognostic systems. Zisman’s group at UCLA successfully integrated stage, grade, and ECOG performance status into a clinically useful tool to stratify RCC patients.\textsuperscript{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.\textsuperscript{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 discriminative 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
Now Enrolling Patients!

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


Study Sponsor:
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Rencarex® is a registered trademark of WILEX AG.
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.

References


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, MD, Dana-Farber Cancer Institute, Boston; David Nanus, MD,Memorial Sloan-Kettering Cancer Center, New York; Sylvie Negrier, MD, CentreLeon 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.”

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 and 1990.
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

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

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 patients 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

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.5

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.

References
The Fifth International Kidney Cancer Symposium

September 22 and 23, 2006
Chicago, Illinois

Kidney Cancer Association
in joint sponsorship with
THE CLEVELAND CLINIC FOUNDATION
The Taussig Cancer Center

For more information about the Kidney Cancer Association and about the Fifth International Kidney Cancer Symposium go to:
www.curekidneycancer.org
www.kidneycancersymposium.com
When health insurance just isn’t enough...

Co-Pay Relief may be the answer. The Patient Advocate Foundation helps insured patients with:

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- Lung Cancer
- Prostate Cancer
- Secondary issues resulting from cancer treatment
- Macular Degeneration
- Kidney Cancer
- Sarcoma

Financial assistance for patients with health insurance.

Many patients facing serious illness just can’t afford all their pharmaceutical treatment expenses - even though they have health insurance, including new Medicare Part D beneficiaries. Some are even forced to choose between paying for their treatment or paying for groceries, utilities and other essentials. That’s where the Patient Advocate Foundation comes in. Through its Co-Pay Relief, *A Patient Assistance Program*, the Patient Advocate Foundation helps cover out-of-pocket co-payments for insured patients who qualify medically and financially.

To find out more about this important program visit copays.org or patientadvocate.org, or call toll-free 866-512-3861.

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Co-Pay Relief
*A Patient Assistance Program*

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866-512-3861
Kidney Cancer Journal Index of Articles 2005

[Editor’s Note: To gain access to an online version of these issues please visit http://www.kidneycancerjournal.org.]

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Surgical Strategies to Optimize Outcomes in Isolated Renal Fossa Recurrence Following Nephrectomy
Peter R. Carroll, MD

Report Card on Adjuvant Therapy: Trials Build Enrollment, Enhancing Prospects for New Treatment Options
Tim Eisen, PhD, FRCP
NEXAVAR® (sorafenib) tablets 200 mg

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION
0911800885, R: 1

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 component of NEXAVAR.

WARNINGs

Common adverse events were monitored in randomised controlled trials and observational studies, and included hypertension, diarrhea, hand-foot skin reaction, fatigue, and rash.

Dose Considerations
NEXAVAR is supplied in a blister pack of 10 tablets.

PATIENT INFORMATION
NEXAVAR is supplied in a blister pack of 10 tablets.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>NEXAVAR N=41</th>
<th>Placbe N=41</th>
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</thead>
<tbody>
<tr>
<td><strong>Any Event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular, General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (3)</td>
<td>2 (1)</td>
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<tr>
<td><strong>Constitutional symptoms</strong></td>
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<td></td>
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<tr>
<td>Fatigue</td>
<td>37 (9)</td>
<td>28 (7)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>10 (2)</td>
<td>6 (1)</td>
</tr>
<tr>
<td><strong>Dermatology/skin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post/desquamation</td>
<td>40 (10)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>30 (7)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>27 (7)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>19 (5)</td>
<td>3 (1)</td>
</tr>
<tr>
<td><strong>Dry skin</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal symptoms</strong></td>
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<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>23 (5)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (4)</td>
<td>12 (3)</td>
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<tr>
<td><strong>Hematology/bleeding</strong></td>
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<tr>
<td>Hemorrhage/Hemostasis</td>
<td>15 (3)</td>
<td>8 (2)</td>
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<tr>
<td><strong>Hypersensitivity</strong></td>
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<tr>
<td><strong>Neurology</strong></td>
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<tr>
<td>Neuritis, sensory neuropathy</td>
<td>13 (3)</td>
<td>6 (2)</td>
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<tr>
<td>Pain</td>
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<td>9 (2)</td>
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<tr>
<td>Pain, abnormal</td>
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<td>Pain, joint</td>
<td>10 (2)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Pain, headache</td>
<td>14 (3)</td>
<td>12 (3)</td>
</tr>
</tbody>
</table>

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 9% of placebo patients).

References:
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.
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)
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