Drugs of the Future 2007, 32(6): 527-536

CCC: 0377-8282/2007
DOI: 10.1358/dof.2007.032.06.1097657

Review Article

New therapies in the treatment of renal cell carcinoma

M. Levin[1*], M. Veliz[2]

*[1]Associate Professor and Interim Chief of Hematology and Oncology, New Jersey Medical School, Newark, NJ 07101, USA; [2]Resident in Medicine, University Hospital, Newark, NJ 07103, USA. *Correspondence: e-mail: levinm1@umdnj.edu*

CONTENTS

Abstract

Metastatic renal cell carcinoma (mRCC) is a disease historically resistant to systemic cancer therapies. For several decades, the biological agents interferon and interleukin were the only available options, but they were fairly toxic and had low efficacy. However, the past several years have witnessed the introduction of novel effective therapies that have radically changed the treatment of metastastic and recurrent RCC. We review the already approved novel agents and discuss therapies in late-stage clinical trials.

Introduction

Metastatic renal cell carcinoma (mRCC) is a disease historically resistant to standard therapy. For several decades, the prognosis of mRCC has remained poor. The only effective treatments have been nephrectomy for patients with resectable tumor and cytokine therapy. However, some advances have recently been made in the understanding of the molecular biology of RCC that have allowed the identification of various pathways and novel targeted therapies that can impede the growth of RCC.

Epidemiology

RCC accounts for approximately 3% of all malignancies and is the third most common urological cancer after prostate and bladder cancers. According to the Surveillance Epidemiology and End Results (SEER) data, the incidence of RCC has increased over the past 3 decades (1). This phenomenon may in part be explained by the increasing detection of presymptomatic tumors, by the extensive use of abdominal imaging methods, such as ultrasonography, computerized tomography and magnetic resonance, leading to an earlier diagnosis and probably better prognosis (2). Approximately 25-40% of clinically diagnosed RCCs are found incidentally and 25-30% of the patients have metastatic disease at initial presentation. The median age at diagnosis is 65 years (1). In developed nations, the average age-adjusted incidence of RCC is approximately 12/100,000 men and 5/100,000 women (3, 4). The American Cancer Society estimated that 38,890 individuals (24,650 men and 14,240 women) would be diagnosed and 12,840 would die of cancer of the kidney and renal pelvis in 2006 (1). The 5-year survival for localized, regionally advanced and metastatic disease is 90%, 61% and only 10%, respectively (5, 6).

Clinicopathological presentation

RCC typically has multiple symptoms at presentation. Small, localized tumors rarely produce symptoms, and for this reason, the diagnosis is often delayed until after the disease is advanced. The most common presentations are hematuria (50-60%), abdominal pain (40%) and palpable abdominal mass (30-40%). These three symptoms occur as the classic triad in only 10% of patients, however. Other patients may have nonspecific signs and symptoms, such as fever, malaise, night sweats and weight loss (7). Due to the rarity of warning signs, approximately 30% of patients present with metastatic disease at the time of diagnosis (8), although in some series this percentage has been as high as 65% (9). RCCs have been classified histologically as clear cell carcinoma (75-85%), chromophilic (12-14%), chromophobic (4-6%), oncocytic (2-4%) and collecting duct tumors (1%) (7).

Therapeutic options

Role of surgery

The primary treatment of RCC consists of radical nephrectomy, and in selected cases partial nephrectomy. In cases of metastatic disease, a nephrectomy can be considered for symptomatic relief of pain, hematuria or

paraneoplastic syndromes such as hypercalcemia (10). Recent randomized studies have shown a survival advantage for patients with good performance status and limited disease burden treated with cytoreductive nephrectomy prior to interferon alfa (IFN-α) compared to those treated immediately with IFN-α without nephrectomy (11-13). Similar results have been obtained in nonrandomized studies using IL-2 (14). The question of whether nephrectomy performed after a response to immunotherapy will be of similar benefit to that performed prior to immunotherapy remains to be addressed (15). Furthermore, resection of metastases in carefully selected patients, particularly those with solitary metastases, can provide a survival benefit (9, 16).

Role of radiotherapy

RCC has historically been considered a radioresistant tumor using conventional radiotherapy and this treatment has mainly been used for the palliation of pain. However, a recent prospective phase II trial using extracranial stereotactic radiotherapy for patients with primary and metastatic RCC resulted in a high local control rate with generally low toxicity. The authors concluded that the method could be considered a therapeutic alternative to surgery in patients with a limited number of metastases, as local treatment or as a method for reducing tumor burden prior to medical treatment (17). However, phase III clinical trials are needed to corroborate these findings.

Role of radiofrequency ablation

Radiofrequency ablation, a procedure that involves percutaneous image-guided ablation with a needle applicator that deposits energy, has been successful in treating selected patients who are poor surgical candidates due to significant morbidities. The data have shown promising short-term results, but long-term survival and disease-free survival data are needed (18, 19).

Role of chemotherapy

RCC is a chemotherapy-resistant tumor that exhibits only a marginal response rate to cytotoxic agents, and no clear survival benefit for chemotherapy over cytokine therapy has yet been demonstrated (6). Therefore, chemotherapy has a limited role in RCC (20).

Evidence from a dated phase II trial of gemcitabine (Gemzar®) indicated that response rates were quite low (21). Researchers from Italy recently conducted a small clinical trial evaluating the combination of gemcitabine, IFN-α and aldesleukin (Proleukin®) in 16 patients with mRCC. Continued therapy with IFN-α and aldesleukin was given to patients who responded to or were stabilized by treatment. One patient achieved a complete disappearance of detectable cancer (complete remission, CR) and 3 patients (28%) achieved at least a 50% reduction in their cancer (partial remission, PR). In addition, 7 patients had their cancer stabilized by treatment. The average time to progression was approximately 14 months and the average survival was approximately 20 months. Treatment was generally well tolerated. The researchers concluded that although this was a small clinical trial, it appears that the addition of gemcitabine to IFN-α and aldesleukin may enhance the anticancer activity in mRCC (22). Future clinical trials involving larger numbers of patients and directly comparing the addition of gemcitabine to IFN-α and aldesleukin compared to IFN-α and aldesleukin alone are warranted.

Cytokine therapy

RCC evokes an immune response, which occasionally results in spontaneous and significant remissions. In an attempt to reproduce or accentuate this response, research over the past two decades has focused on two cytokines that have consistently shown antitumor activity in RCC: IFN-α and IL-2 (23).

1. IFN-α

Recent studies have suggested that IFN-α, despite having limited antitumor activity, may produce a modest impact on survival. IFN-α administered as a single agent in mRCC provides a response rate of between 8% and 26%, with a complete response rate of 2-7% (10, 24-29). The interval between the start of treatment and the occurrence of a clinical response is around 1-3 months (10). The median duration of response in CR/PR patients ranges from 10 to 16 months, but rare cases of long-lasting remission have been described (10, 29). Median overall survival ranges from 13 to 25 months (29-32). In the case of an objective response or disease stabilization, treatment is usually continued for a year (10), although treatment for up to 2 years seems to be beneficial and may improve the outcome (29). The most frequent side effects are flu-like symptoms such as fever, chills, headache and myalgias, and acetaminophen is usually given at the start of therapy to ameliorate these symptoms. Less frequent side effects include neutropenia, depression, neurotoxicity, elevated liver enzymes and thyroid dysfunction (10). Most adverse effects, especially the flu-like symptoms, tend to diminish over time during long-term therapy. Although no clear dose-response relationship exists, doses in the 5-10 MU/m^2 range appear to have the highest therapeutic index (23). A recent study suggested that the use of low-dose IFN-α given twice daily yields similar response rates but less toxicity compared with daily intermediate-dose IFN-α (30). Combinations of IFN-α with 13-*cis*-retinoic acid (32) and with several chemotherapeutic agents, such as vinblastine, epirubicin (33, 34), cyclophosphamide (35, 36), ifosfamide, vindesine (37) and floxuridine (38, 39), have shown no additional benefit. Overall, IFN-α provides a modest survival benefit compared to placebo and other commonly used treatments, and should be considered for the controlled arm of futures studies of systemic therapies (6, 31, 40).

2. IL-2

Rosenberg *et al.* reported in 1985 the first study of the administration of IL-2 showing an objective response in metastatic cancer (41). Since then, several studies have reported a response rate in RCC ranging from 7% to 26% (28, 42-51), a median survival ranging from 10 to 20 months (45-48, 50) and a 5-year survival rate of approximately 8% (47). A 10-year follow-up study of 255 patients treated with high-dose recombinant human IL-2 showed that patients who achieved a CR that lasted more than 30 months and those with PR resected to "no evidence of disease" after a response to high-dose IL-2 were unlikely to progress and may actually be cured (23, 52). Inpatient high-dose bolus administration of IL-2 was approved by the Food and Drug Administration (FDA) in 1992 for the treatment of patients with stage IV RCC (23). Although inpatient high-dose bolus IL-2 produces a favorable outcome, it is also associated with significant toxicities that affect essentially every organ system. Patients uniformly develop fever, chills and malaise, as well as vascular leak syndrome characterized by weight gain, oliguria, tachycardia and hypotension. Cardiopulmonary (arrhythmias, ischemic injury, lymphocytic myocarditis), hematological (anemia, leukopenia and thrombocytopenia), gastrointestinal (nausea, vomiting, diarrhea, mucositis) and dermatological toxicities (erythema, pruritus and generalized erythroderma) are frequently seen (53-55). The toxic effects of IL-2 are more pronounced than those of IFN-α, are largely dependent on the dose and schedule used, and are generally reversible with discontinuation of therapy (50). Several phase II studies have demonstrated that administering lower doses of IL-2 by i.v. bolus or continuous i.v. infusion or s.c. with or without IFN-α produces overall response rates similar to those with high-dose IL-2 therapy, but responses appeared to be less durable than those seen with high-dose regimens (51, 54, 55). The Cytokine Working Group performed a prospective randomized phase III trial to determine the value of outpatient IL-2 and IFN-α relative to high-dose IL-2 in patients with mRCC (56). The study showed a significantly higher response rate in the high-dose i.v. IL-2 group (23.2%) *versus* the s.c. IL-2 and IFN-α group (9.9%). For patients with bone or liver metastasis ($p = 0.002$) or primary tumors ($p = 0.54$), survival was superior in the high-dose IL-2 arm, whereas no significant survival differences between the two arms were noted for patients who had undergone prior nephrectomy or who had no bone or liver metastasis. Another three-arm randomized phase III trial comparing high-dose i.v. IL-2 *versus* low-dose i.v. or s.c. IL-2 also showed higher response rates in the high-dose group, but there were no overall survival differences. However, the toxicity was significantly less in the low-dose subgroup. Response durability and survival in patients with CR was superior in the high-dose i.v. IL-2 compared with the low-dose i.v. group (57). These data raise the question of efficacy *versus* toxicity.

Recent efforts have focused on the identification of factors predictive of response to IL-2 therapy so that this treatment could be limited to those most likely to benefit. A study that evaluated the correlation between histopathological features of RCC and the response rates to IL-2 showed a response rate for patients with clear cell (especially in the presence of alveolar features and the absence of papillary and granular features) of 21% *versus* 6% for patients with variant- or indeterminate-type RCC ($p = 0.20$). The study suggested that patients with non-clear cell RCC or clear cell RCC with papillary, no alveolar and/or more than 50% granular features respond poorly to IL-2 and should be considered for alternative treatments (58). Recently, carbonic anhydrase IX (CAIX) has been identified as a molecular marker that is predictive of response to IL-2 therapy (59, 60). Investigation of other tumor-related predictors of IL-2 responsiveness is warranted.

The von Hippel-Lindau (VHL) tumor suppressor gene

VHL syndrome is an autosomal dominant disorder associated with increased susceptibility to vascular tumors, including hemangioblastoma of the retina and central nervous system (CNS) and clear cell renal carcinoma. The VHL gene is mutated in 50-60% of sporadic clear cell renal carcinoma cases (61-64). VHL mutations are not found in association with other subtypes of renal cancer, such as papillary, chromophobic and collecting duct carcinomas and the essentially benign oncocytomas (65, 66). An inactivated VHL gene inherited from either parent causes VHL disease. The development of tumors in VHL disease is linked to loss of the remaining normal VHL allele in a susceptible cell, thereby eliminating the VHL gene product (pVHL) (67).

It was recently discovered that pVHL is an important regulator of hypoxia-inducible factor (HIF). Downregulation of HIF appears to be both necessary and sufficient for renal tumor suppression by pVHL (68, 69). When oxygen is available, pVHL binds HIF-α, signaling the destruction of HIF-α. Hypoxic cells or cells lacking pVHL accumulate high levels of HIF, which activates the transcription of a variety of genes, including vascular endothelial growth factor (VEGF), platelet-derived growth factor-β (PDGF-β), basic fibroblast growth factor (bFGF), transforming growth factor-α (TGF-α) and erythropoietin (68-70). These growth factors play an important role in angiogenesis and therefore in tumor progression, and in paraneoplastic symptoms. They function in a paracrine loop by binding to specific receptors present on the surface of endothelial cells and vascular pericytes. Binding of these receptors results in stimulation of receptor tyrosine kinases, eventually leading to cell proliferation and angiogenesis. The overproduction of erythropoietin accounts for the association of paraneoplastic erythrocytosis that occurs in patients with kidney cancer (68). Overexpression of TGF-α and its receptor EGFR (epidermal growth factor receptor) has been observed in numerous RCC tumors and cell lines. TGF-α, which is a strong mitogen for tumor cells, has been demonstrated to support RCC cell growth through an autocrine loop (71, 72).

In addition, RCC expresses high levels of PDGF (73), which is important for the survival of pericytes, promoting tumor growth and angiogenesis (67). Although not all patients with RCC have VHL mutations, nearly all patients with RCCs of the clear cell subtype demonstrate overexpression of VEGF, which has been used to explain the increased vascularity of RCC (74, 75). This also suggests that alternative pathways independent of VHL can promote VEGF expression and are likely to be involved in the oncogenesis of RCC. Since RCC is a highly vascularized tumor and angiogenesis plays a crucial role in the growth of cancer cells, inhibition of the above-mentioned growth factors has been pursued in recent years as a therapeutic strategy in RCC. In several studies, the potential of this approach is emerging, as discussed below.

Antiangiogenic drugs

1. Thalidomide and analogues

Thalidomide is an agent with complex antiangiogenic and immunomodulatory properties. It has been demonstrated to reduce mRNA and protein expression of bFGF and VEGF, with resulting inhibitory effects on endothelial cell proliferation (76-79). In addition, thalidomide has multiple other mechanisms resulting in antitumor effects, including reduction in tumor necrosis factor-α (TNF-α) production from macrophages (80-84) and induction of G1 cell cycle arrest and apoptosis (85). Several small studies of thalidomide as a single agent in RCC have reported no CRs, PRs ranging from 0% to 17% and stable disease in 17-64% of patients (86-92). Progression-free survival was not reported. In these studies, thalidomide was generally started at a low dose of 100-200 mg/day and escalated to higher doses until toxicity was observed. Grade 3 or higher toxicity included neuropathy (4-30%), thromboembolic events (3-23%), sedation (3-23%), fatigue (3-15%) and constipation (4-9%).

Thalidomide has also been investigated in combination with standard cytokine therapy and chemotherapy. A phase II trial studying the combination of thalidomide and IFN-α showed no CRs, a PR rate of 22% and stable disease in 63% of patients for 3 months or longer. The median time to treatment failure was 7.7 months and median survival time was 14.9 months (93). In a similar small trial in 30 patients, there were no CRs, 2 patients had a PR (6.7%), 8 had stable disease (26.7%) and 11 (including 1 patient with an initial PR) had disease progression (36.7%). The median survival was 68 weeks (94).

A recent study by Sella *et al.* showed more promising results. A PR was achieved in 21.4% of patients and 50% had stable disease, with an overall nonprogression rate of 71.4%. Mean overall survival was 17.4 months (95). However, another phase II study showed no response to treatment (96) and was terminated early due to unacceptable neurotoxic side effects that included seizures, neuropathy and stroke-like symptoms (97). A randomized phase III trial of low-dose interferon alone *versus* combination with escalating doses of thalidomide that enrolled 353 patients showed no overall survival advantage for the addition of thalidomide to interferon, although progression-free survival was statistically significantly longer in the interferon plus thalidomide arm. Quality of life was worse in the patients being treated with the combination due to fatigue, myelosuppression and thrombotic events (98).

The combination of thalidomide with IL-2 has also been explored. Results of various phase I/II studies have shown an overall response rate of 0-6% (99-101). However, 52% of patients in a phase I/II study by Amato *et al.* experienced disease control: 8% had CRs, 29% PRs and 15% stable disease. In the same study, disease progression was observed in 24 patients (47%). Survival in the two phases ranged from 4 weeks to 45.2+ months (102). The reason for the discrepancy between this study and previous studies is unclear.

Investigators have also examined the combination of thalidomide with chemotherapeutic agents in patients with mRCC. The addition of thalidomide to 5-fluorouracil (5-FU) and gemcitabine in a phase II study including 21 patients showed an overall response rate of 10%, with no CRs and an increased incidence of venous thromboembolic events. The authors concluded that this three-drug regimen did not improve the objective response rate previously observed with gemcitabine and 5-FU alone and added significant vascular toxicity (103).

Lenalidomide (Revlimid®) is a structural and functional analogue of thalidomide that has demonstrated enhanced immunomodulatory properties and a more favorable toxicity profile. An open-label phase II study of lenalidomide in patients with mRCC that included 28 patients showed a durable PR rate of 11%. Further studies will be required to assess the overall activity of lenalidomide in patients with mRCC (104).

Researchers from the Cleveland Clinic recently conducted a clinical trial evaluating lenalidomide in the treatment of mRCC in 28 patients. More than half of the patients had received prior systemic (full body) therapy, 40% had received prior irradiation and 43% had received no therapy besides surgery. Three patients achieved a partial disappearance of their cancer that persisted for over 15 months; 39% of patients had stabilization of their cancer for at least 3 months. Median overall survival had not yet been reached at 13.5 months of follow-up. Major side effects included fatigue, skin problems and low levels of immune cells. The authors concluded that lenalidomide appears promising for the treatment of mRCC (104). Future clinical trials will help evaluate the true efficacy of lenalidomide in mRCC.

2. Neovastat (AE-941)

Neovastat is a natural occurring antiangiogenic compound prepared by homogenization and purification of shark cartilage. Neovastat is orally bioavailable and shows significant antitumor and antimetastatic properties in animal models (105). In addition to its ability to induce endothelial cell apoptosis (106) and inhibit matrix metalloproteinase activities (107), Neovastat has been found to inhibit several VEGF-dependent processes, including

endothelial cell migration, vasculogenesis and vascular permeability, through competitive binding with VEGFR-2 (105, 108).

A phase II trial of Neovastat showed a 9% overall response rate (109). However, this drug failed to provide any survival benefit compared to placebo in a large international phase III trial conducted in 302 patients with mRCC refractory to first-line immunotherapy (110).

3. Bevacizumab (Avastin®)

Bevacizumab is a recombinant human monoclonal antibody against all isoforms of VEGF (111). Phase I studies of bevacizumab in patients with advanced malignancies have shown no treatment-related grade 3 or 4 adverse events (112, 113). A subsequent randomized, double-blind phase II trial in patients with metastatic renal cancer compared bevacizumab with placebo (114). A total of 116 patients were randomly assigned to receive placebo, low-dose (3 mg/kg) bevacizumab or high-dose (10 mg/kg) bevacizumab given intravenously every 2 weeks. All patients had histologically confirmed clear cell-type renal cancer and either had received previous therapy with IL-2 or had a contraindication for its use. The primary endpoint was time to progression (TTP) of disease. Only 4 patients (10%) had objective responses, all of which were PRs and all in the high-dose bevacizumab arm. There was a significant prolongation of the TTP of disease in the high-dose group (4.8 months) as compared with the placebo group (2.4 months), and a small difference, of borderline significance, between the TTP of disease in the low-dose group compared with the placebo group. The study was stopped early in view of the observed significant differences in TTP. There were no significant differences in overall survival among groups, which was attributed to the crossover design. There were no life-threatening toxic effects or deaths attributable to bevacizumab. Hypertension and asymptomatic proteinuria without renal insufficiency were the most frequent side effects. All toxicities were reversible upon cessation of therapy (114). Patients with disease progression in the placebo group were eligible to enter a separate pilot study in which they received low-dose bevacizumab alone or low-dose bevacizumab plus escalating doses of thalidomide to the maximum tolerated dose by the patient. There were no objective responses and no differences in progression-free survival between groups (2.4 months for bevacizumab alone *vs.* 3.0 months for bevacizumab plus thalidomide; $p = 0.63$) (115).

Based on the results of the above study, a randomized, multicenter phase III trial comparing IFN-α alone to the combination of bevacizumab plus IFN-α in previously untreated patients with mRCC was conducted by the Cancer and Leukemia Group B 90206 (116). Patients with metastatic clear cell RCC who had not received any prior systemic therapy of any kind were eligible. Patients were randomized to receive low-dose IFN-α (9 MU 3 times weekly) plus placebo or the same dose and schedule of IFN-α plus bevacizumab 10 mg/kg i.v. every 2 weeks. The study was originally designed to measure an improvement in overall survival. However, in prior consultation with the FDA, the primary analysis endpoint was revised to assess improvement in progression-free survival (117). The study enrolled 649 patients with first-line mRCC. Interim analysis showed that bevacizumab in combination with IFN-α in patients with first-line mRCC met the primary analysis endpoint by significantly improving progression-free survival compared to IFN-α therapy alone. In addition, the early analysis indicated a trend toward improvement in overall survival in the combination arm (117). Final results of the study have yet to be published.

According to updated results from a phase II clinical trial presented at the 23rd Annual Chemotherapy Foundation Symposium, treatment with the combination of erlotinib (Tarceva®) and bevacizumab resulted in good survival among patients with mRCC (118).

Current guidelines recommend bevacizumab as an option for crossover therapy of RCC after first-line therapy with IL-2, sorafenib or sunitinib (40).

4. VEGF $Trap_{R1R2}$

VEGF $Trap_{R1R2}$ (aflibercept) is a fusion protein engineered by combining the VEGFR-1 immunoglobulin domain 2 and the VEGFR-2 immunoglobulin domain 3 fused to the Fc portion of human IgG_1. This entirely human molecule, which binds VEGF 100-1,000-fold more tightly than monoclonal antibodies, has been shown to inhibit the growth and vascularity of a variety of subcutaneously (s.c.) implanted tumor cells in mouse models (119).

A phase I trial of VEGF Trap was conducted in patients with relapsed or refractory solid tumors. Patients received a single s.c. dose of VEGF Trap, followed 4 weeks later by 6 weekly doses. No objective responses were observed, but 14 of 24 evaluable patients, including 5 of 6 treated at the highest dose level, maintained stable disease for at least 10 weeks and entered the extension study. Drug-related grade 3 adverse events included hypertension, proteinuria and afebrile neutropenia (120). Further studies investigating the effects of this drug in patients with mRCC are needed.

5. Sunitinib and sorafenib

Sunitinib (SU-11248, Sutent®) is an oral multitargeted receptor tyrosine kinase inhibitor of VEGF and PDGF (121). Two phase I trials of sunitinib in patients with malignancies not amenable to conventional therapy showed PRs in several cancers, including RCC. From these studies, a dose of 50 mg daily for 4 weeks followed by 2 weeks off was recommended for phase II investigation. Overall, the agent was well tolerated, with grade 3 or 4 fatigue/asthenia and hypertension being the dose-limiting side effects, which were reversible upon discontinuation of therapy (122, 123). A subsequent open-label phase II trial that included 63 cytokine-refractory mRCC patients showed that 40% of patients had a PR and 27% had stable disease lasting at least 3 months. Median time to progression was 8.7 months and median overall survival was 16.4 months. In this trial, sunitinib was generally well tolerated, with a compliance rate during the first 6 months of

treatment of at least 95%. Grade 2 or 3 fatigue was the most common dose-limiting adverse event (38%). Other grade 2 or 3 side effects included diarrhea (24%), nausea (19%) and stomatitis (19%). A rarer complication included erythema of the palms and soles of the feet (8%) (124).

A larger, multicenter phase II follow-up trial included 106 patients with mRCC who had disease progression despite cytokine therapy. According to the investigator assessment, 45 (43%) patients achieved a PR and 1 (1%) patient achieved a CR, for an overall response rate of 44%. An additional 23 patients (22%) had stable disease for at least 3 months. The median duration of response was 10 months and the median progression-free survival was 8.1 months. An independent third-party assessment concluded that 36 patients had a PR (34%) and that the median progression-free survival was 8.3 months. The most common adverse events experienced by patients were fatigue (28%) and diarrhea (20%). The most common laboratory abnormalities were neutropenia (42%), elevation of lipase (28%) and anemia (26%) (125).

Preliminary results from an open-label, multicenter phase II study of an alternative regimen of sunitinib administered continuously at a daily dose of 37.5 mg to 88 patients showed some tumor shrinkage in the majority of patients evaluated at 4 weeks, with 3 initial PRs. The most commonly reported adverse events were mucositis, fatigue, hair/skin discoloration and hand-foot syndrome. Sunitinib was generally well tolerated, with only a few patients requiring treatment breaks and/or dose reduction (126).

An international, randomized phase III trial comparing sunitinib (administered in 6-week cycles of 50 mg daily for 4 weeks, then 2 weeks off) with IFN-α (9 MU s.c. 3 times weekly) as first-line treatment in 750 patients with clear cell mRCC showed that the median progression-free survival was significantly longer in the sunitinib group (11 months) than in the IFN-α group (5 months). Sunitinib was also associated with a higher objective response rate than IFN-α (31% *vs.* 6%; $p < 0.001$). The proportion of patients with grade 3 or 4 treatment-related fatigue was significantly higher in the group treated with IFN-α, whereas diarrhea was more frequent in the sunitinib group. Patients in the sunitinib group reported a significantly better quality of life than did patients in the IFN-α group (127). The results of this study demonstrated a significant improvement in progression-free survival and objective response rate for sunitinib over IFN-α, and based on these results, sunitinib is standard therapy for the first-line treatment of mRCC.

Sorafenib is a Raf kinase inhibitor and a VEGF receptor tyrosine kinase inhibitor. The evidence supporting sorafenib (Nexavar®) is similar and was published at the same time as that for sunitinib (128).

6. Temsirolimus

Temsirolimus (Torisel™) is a mammalian target of rapamycin (mTOR) inhibitor. It resulted in improved overall survival in a phase III study in RCC (129). Temsirolimus is not yet available, but is currently awaiting approval following filing of an NDA in October 2006.

7. In the pipeline

Several other biologicals are being investigated for the treatment of RCC, including lapatinib (Tykerb®), erlotinib (Tarceva®), gefitinib (Iressa®), semaxanib, axitinib, vatalanib (PTK-787/ZK-222584) and atrasentan (Xinlay™). Immunotherapy approaches under investigation include dendritic cells, allogeneic stem cell transplantation and monoclonal antibodies targeting G250 (Rencarex®), IL-6, TNF-α (infliximab, Remicade®) and heat shock protein (HSP).

Conclusions

The past several years have witnessed the emergence of a variety of different agents for the treatment of RCC. Some have already been approved by regulatory bodies in the U.S.A. and Europe, while others are still under investigation. We look forward to continuous advancement in the available options for treating RCC in the coming years.

References

1. Ries, L.A.G., Harkins, D., Krapcho, M. et al. (Eds). SEER Cancer Statistics Review, 1975-2003, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2003/, based on November 2005 SEER data submission, posted to the SEER web site, 2006.

2. Chow, W., Devesa, S.S., Warren, J.L., Fraumeni, J.F. *Rising incidence of renal cell cancer in the United States.* JAMA – J Am Med Assoc 1999, 281: 1628-31.

3. Mickisch, G., Carballido, J., Hellsten, S., Schulze, H., Mensink, H. *Guidelines on renal cell cancer*. Eur Urol 2001, 40(3): 252-5.

4. Patel, P.H., Chaganti, R.S.K., Motzer, R.J. *Targeted therapy for metastatic renal cell carcinoma*. Br J Cancer 2006, 94(5): 614-9.

5. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 17 Regs Public-Use, Nov 2005 Sub (1973-2003 varying), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2006, based on the November 2005 submission.

6. Motzer, R.J., Mazumdar, M., Bacik, J., Russo, P., Berg, W.J., Metz, E.M. *Effect of cytokine therapy on survival for patients with advanced renal cell carcinoma*. J Clin Oncol 2000, 18(9): 1928-35.

7. Motzer, R.J., Bander, N.H., Nanus, D.M. *Renal-cell carcinoma*. N Engl J Med 1996, 335(12): 865-75.

8. Vogelzang, N.J., Scardino, P.T., Shipley, W.U., Debruyne, F.M.J., Linehan, W.M. (Eds.). Comprehensive Textbook of Genitourinary Oncology, 3rd Ed. Kidney Cancer: Signs, Symptoms and Paraneoplastic Syndromes of Renal Cell Carcinoma. Lippincott Williams & Wilkins, 2006.

9. Vogl, U.M., Zehetgruber, H., Dominkus, M., Hejna, M., Zielinski, C.C., Haitel, A., Schmidinger, M. *Prognostic factors in*

metastatic renal cell carcinoma: Metastasectomy as independent prognostic variable. Br J Cancer 2006, 95(6): 691-8.

10. Van Spronsen, D.J., Mulders, P.F.A., De Mulder, P.H.M. *Novel treatments for metastatic renal cell carcinoma*. Crit Rev Oncol Hematol 2005, 55(3): 177-91.

11. Flanigan, R.C., Salmon, S.E., Blumenstein, B.A. et al. *Nephrectomy followed by interferon-alpha-2b compared with interferon-alpha-2b alone for metastatic renal-cell cancer*. N Engl J Med 2001, 345(23): 1655-9.

12. Mickisch, G.H., Garin, A., van Poppel, H., de Prijck, L., Sylvester, R., European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. *Radical nephrectomy plus interferon-alpha-based immunotherapy compared with interferon alpha alone in metastatic renal-cell carcinoma: A randomised trial*. Lancet 2001, 358: 966-70.

13. Flanigan, R.C., Mickisch, G., Sylvester, R., Tangen, C., Van Poppel, H., Crawford, E.D. *Cytoreductive nephrectomy in patients with metastatic renal cancer: A combined analysis*. J Urol 2004, 171(3): 1071-6.

14. Figlin, R., Gitlitz, B., Franklin, J. *Interleukin-2-based immunotherapy for the treatment of metastatic renal cell carcinoma: An analysis of 203 consecutively treated patients*. Cancer J Sci Am 1997, 3(Suppl. 1): S92-7.

15. Flanigan, R.C. *Debulking nephrectomy in metastatic renal cancer.* Clin Cancer Res 2004, 10(18, Pt. 2): 6335S-41.

16. Kavolius, J.P., Mastorakos, D.P., Pavlovich, C., Russo, P., Burt, M.E., Brady, M.S. *Resection of metastatic renal cell carcinoma*. J Clin Oncol 1998, 16(6): 2261-6.

17. Svedman, C., Sandstrom, P., Pisa, P. et al. *A prospective phase II trial of using extracranial stereotactic radiotherapy in primary and metastatic renal cell carcinoma*. Acta Oncol 2006, 45(7): 870-5.

18. Gervais, D.A., Arellano, R.S., Mueller, P.R. *Percutaneous radiofrequency ablation of renal cell carcinoma.* Eur Radiol 2005, 15(5): 960-7.

19. Boss, A., Clasen, S., Kuczyk, M., Schick, F., Pereira, P.L. *Image-guided radiofrequency ablation of renal cell carcinoma.* Eur Radiol 2007, 17(3): 725-33.

20. Hartmann, J.T., Bokemeyer, C. *Chemotherapy for renal cell carcinoma*. Anticancer Res 1999, 19(2C): 1541-3.

21. DeMulder, P.H., Weissbach, L., Jakse, G. et al. *Gemcitabine: A phase II study in patients with advanced renal cancer.* Cancer Chemother Pharmacol 1996, 37: 491-5.

22. Neri, B., Doni, L., Gemelli, M. et al. *Phase II trial of weekly intravenous gemcitabine administration with interferon and interleukin-2 immunotherapy for metastatic renal cell cancer*. J Urol 2002, 168: 956-8.

23. Atkins, M.B., Regan, M., McDermott, D. *Update on the role of interleukin 2 and other cytokines in the treatment of patients with stage IV renal carcinoma*. Clin Cancer Res 2004, 10(18, Pt. 2): 6342S-6S.

24. Krown, S.E. *Interferon treatment of renal cell carcinoma. Current status and future prospects*. Cancer 1987, 59(3, Suppl.): 647-51.

25. Muss, H.B., Costanzi, J.J., Leavitt, R. et al. *Recombinant alfa interferon in renal cell carcinoma: A randomized trial of two routes of administration*. J Clin Oncol 1987, 5(2): 286-91.

26. Trump, D.L., Elson, P.J., Borden, E.C. et al. *High-dose lymphoblastoid interferon in advanced renal cell carcinoma: An Eastern Cooperative Oncology Group Study*. Cancer Treat Rep 1987, 71(2): 165-9.

27. Minasian, L.M., Motzer, R.J., Gluck, L., Mazumdar, M., Vlamis, V., Krown, S.E. *Interferon alfa-2a in advanced renal cell carcinoma: Treatment results and survival in 159 patients with long-term follow-up*. J Clin Oncol 1993, 11(7): 1368-75.

28. Negrier, S., Escudier, B., Lasset, C. et al. *Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Francais d'Immunotherapie.* N Engl J Med 1998, 338(18): 1272-8.

29. Kankuri, M., Pelliniemi, T.T., Pyrhonen, S., Nikkanen, V., Helenius, H., Salminen, E. *Feasibility of prolonged use of interferon-alpha in metastatic kidney carcinoma: A phase II study*. Cancer 2001, 92(4): 761-7.

30. Tannir, N.M., Cohen, L., Wang, X. et al. *Improved tolerability and quality of life with maintained efficacy using twice-daily low-dose interferon-alpha-2b: Results of a randomized phase II trial of low-dose versus intermediate-dose interferon-alpha-2b in patients with metastatic renal cell carcinoma*. Cancer 2006, 107(9): 2254-61.

31. Motzer, R.J., Bacik, J., Murphy, B.A., Russo, P., Mazumdar, M. *Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma*. J Clin Oncol 2002, 20(1): 289-96.

32. Motzer, R.J., Murphy, B.A., Bacik, J. et al. *Phase III trial of interferon alfa-2a with or without 13-cis-retinoic acid for patients with advanced renal cell carcinoma*. J Clin Oncol 2000, 18(16): 2972-80.

33. Pyrhonen, S., Salminen, E., Ruutu, M. et al. *Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer*. J Clin Oncol 1999, 17(9): 2859-67.

34. Panetta, A., Martoni, A., Guaraldi, M., Tamberi, S., Casadio, M., Lelli, G., Pannuti, F. *Combined chemo-immuno-hormonotherapy of advanced renal cell carcinoma.* J Chemother 1994, 6: 349-53.

35. Wadler, S., Einzig, A.I., Dutcher, J.P., Ciobanu, N., Landau, L., Wiernik, P.H. *Phase II trial of recombinant alpha-2b-interferon and low-dose cyclophosphamide in advanced melanoma and renal cell carcinoma.* Am J Clin Oncol 1988, 11(1): 55-9.

36. Wersall, J.P., Masucci, G., Hjelm, A.L. et al. *Low dose cyclophosphamide, alpha-interferon and continuous infusions of interleukin-2 in advanced renal cell carcinoma*. Med Oncol Tumor Pharmacother 1993, 10(3): 103-11.

37. Konig, H.J., Gutmann, W., Weissmuller, J. *Ifosfamide, vindesine and recombinant alpha-interferon combination chemotherapy for metastatic renal cell carcinoma*. J Cancer Res Clin Oncol 1991, 117(Suppl. 4): S221-3.

38. Falcone, A., Cianci, C., Pfanner, E. et al. *Treatment of metastatic renal cell carcinoma with constant-rate floxuridine infusion plus recombinant alpha 2b-interferon*. Ann Oncol 1996, 7(6): 601-5.

39. Soori, G.S., Schulof, R.S., Stark, J.J., Wiemann, M.C., Honeycutt, P.J., Church, C.K., DePriest, C.B. *Continuous-infusion floxuridine and alpha interferon in metastatic renal cancer: A National Biotherapy Study Group phase II study*. Cancer Invest 1999, 17(6): 379-84.

40. Coppin, C., Porzsolt, F., Awa, A., Kumpf, J., Coldman, A., Wilt, T. *Immunotherapy for advanced renal cell cancer.* Cochrane Database Syst Rev 2005, (1): CD001425.

41. Rosenberg, S.A., Lotze, M.T., Muul, L.M. et al. *Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer*. N Engl J Med 1985, 313(23): 1485-92.

42. Rosenberg, S.A., Yang, J.C., Topalian, S.L. et al. *Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2*. JAMA – J Am Med Assoc 1994, 271(12): 907-13.

43. Royal, R.E., Steinberg, S.M., Krouse, R.S. et al. *Correlates of response to IL-2 therapy in patients treated for metastatic renal cancer and melanoma.* Cancer J Sci Am 1996, 2(2): 91-8.

44. Gore, M.E., Galligioni, E., Keen, C.W., Sorio, R., Loriaux, E.M., Grobben, H.C., Franks, C.R. *The treatment of metastatic renal cell carcinoma by continuous intravenous infusion of recombinant interleukin-2.* Eur J Cancer 1994, 30A(3): 329-33.

45. Whitehead, R.P., Wolf, M.K., Solanki, D.L. et al. *A phase II trial of continuous-infusion recombinant interleukin-2 in patients with advanced renal cell carcinoma: A Southwest Oncology Group study*. J Immunother Emphasis Tumor Immunol 1995, 18(2): 104-14.

46. Gold, P.J., Thompson, J.A., Markowitz, D.R., Neumann, S., Fefer, A. *Metastatic renal cell carcinoma: Long-term survival after therapy with high-dose continuous-infusion interleukin-2*. Cancer J Sci Am 1997, 3(Suppl. 1): S85-91.

47. Negrier, S., Maral, J., Drevon, M., Vinke, J., Escudier, B., Philip, T. *Long-term follow-up of patients with metastatic renal cell carcinoma treated with intravenous recombinant interleukin-2 in Europe.* Cancer J Sci Am 2000, 6(Suppl. 1): S93-8.

48. Libra, M., Talamini, R., Crivellari, D. et al. *Long-term survival in patients with metastatic renal cell carcinoma treated with continuous intravenous infusion of recombinant interleukin-2: The experience of a single institution*. Tumori 2003, 89(4): 400-4.

49. Geertsen, P.F., Gore, M.E., Negrier, S., Tourani, J.M., von der Maase, H. *Safety and efficacy of subcutaneous and continuous intravenous infusion rIL-2 in patients with metastatic renal cell carcinoma.* Br J Cancer 2004, 90(6): 1156-62.

50. Fyfe, G., Fisher, R.I., Rosenberg, S.A., Sznol, M., Parkinson, D.R., Louie, A.C. *Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy*. J Clin Oncol 1995, 13(3): 688-96.

51. Dutcher, J.P., Atkins, M., Fisher, R. et al. *Interleukin-2-based therapy for metastatic renal cell cancer: The Cytokine Working Group experience, 1989-1997*. Cancer J Sci Am 1997, 3(Suppl. 1): S73-8.

52. Fyfe, G.A., Fisher, R.I., Rosenberg, S.A., Sznol, M., Parkinson, D.R., Louie, A.C. *Long-term response data for 255 patients with metastatic renal cell carcinoma treated with high-dose recombinant interleukin-2 therapy*. J Clin Oncol 1996, 14(8): 2410-1.

53. Bukowski, R.M. *Natural history and therapy of metastatic renal cell carcinoma: The role of interleukin-2.* Cancer 1997, 80(7): 1198-220.

54. Dutcher, J. *Current status of interleukin-2 therapy for metastatic renal cell carcinoma and metastatic melanoma*. Oncology (Williston Park) 2002, 16(11, Suppl. 13): 4-10.

55. Dutcher, J.P., Fisher, R.I., Weiss, G. et al. *Outpatient subcutaneous interleukin-2 and interferon-alpha for metastatic renal cell cancer: Five-year follow-up of the Cytokine Working Group Study*. Cancer J Sci Am 1997, 3(3): 157-62.

56. McDermott, D.F., Regan, M.M., Clark, J.I. et al. *Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma*. J Clin Oncol 2005, 23(1): 133-41.

57. Yang, J.C., Sherry, R.M., Steinberg, S.M. et al. *Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer*. J Clin Oncol 2003, 21(16): 3127-32.

58. Upton, M.P., Parker, R.A., Youmans, A., McDermott, D.F., Atkins, M.B. *Histologic predictors of renal cell carcinoma response to interleukin-2-based therapy*. J Immunother 2005, 28(5): 488-95.

59. Bui, M.H., Seligson, D., Han, K.R. et al. *Carbonic anhydrase IX is an independent predictor of survival in advanced renal clear cell carcinoma: Implications for prognosis and therapy*. Clin Cancer Res 2003, 9(2): 802-11.

60. Atkins, M., Regan, M., McDermott, D. et al. *Carbonic anhydrase IX expression predicts outcome of interleukin 2 therapy for renal cancer.* Clin Cancer Res 2005, 11(10): 3714-21.

61. Gnarra, J.R., Tory, K., Weng, Y. et al. *Mutations of the VHL tumour suppressor gene in renal carcinoma*. Nat Genet 1994, 7(1): 85-90.

62. Yao, M., Yoshida, M., Kishida, T. et al. *VHL tumor suppressor gene alterations associated with good prognosis in sporadic clear-cell renal carcinoma*. J Natl Cancer Inst 2002, 94(20): 1569-75.

63. Turner, K.J., Moore, J.W., Jones, A. et al. *Expression of hypoxia-inducible factors in human renal cancer: Relationship to angiogenesis and to the von Hippel-Lindau gene mutation*. Cancer Res 2002, 62(10): 2957-61.

64. Rini, B.I., Jaeger, E., Weinberg, V. et al. *Clinical response to therapy targeted at vascular endothelial growth factor in metastatic renal cell carcinoma: Impact of patient characteristics and Von Hippel-Lindau gene status.* BJU Int 2006, 98(4): 756-62.

65. Gallou, C., Joly, D., Mejean, A. et al. *Mutations of the VHL gene in sporadic renal cell carcinoma: Definition of a risk factor for VHL patients to develop an RCC*. Hum Mutat 1999, 13(6): 464-75.

66. Yoshida, M., Yao, M., Ishikawa, I. et al. *Somatic von Hippel-Lindau disease gene mutation in clear-cell renal carcinomas associated with end-stage renal disease/acquired cystic disease of the kidney*. Genes Chromosomes Cancer 2002, 35(4): 359-64.

67. George, D.J., Kaelin, W.G. Jr. *The von Hippel-Lindau protein, vascular endothelial growth factor, and kidney cancer.* N Engl J Med 2003, 349(5): 419-21.

68. Kaelin, W.G. Jr. *The von Hippel-Lindau tumor suppressor gene and kidney cancer*. Clin Cancer Res 2004, 10(18, Pt. 2): 6290S-5S.

69. Kaelin, W.G. *The von Hippel-Lindau tumor suppressor protein: Roles in cancer and oxygen sensing*. Cold Spring Harb Symp Quant Biol 2005, 70: 159-66.

70. Mellado, B., Gascon, P. *Molecular biology of renal cell carcinoma.* Clin Transl Oncol 2006, 8(10): 706-10.

71. Knebelmann, B., Ananth, S., Cohen, H.T., Sukhatme, V.P. *Transforming growth factor alpha is a target for the von Hippel-Lindau tumor suppressor*. Cancer Res 1998, 58(2): 226-31.

72. de Paulsen, N., Brychzy, A., Fournier, M.C., Klausner, R.D., Gnarra, J.R., Pause, A., Lee, S. *Role of transforming growth factor-alpha in von Hippel-Lindau (VHL)(-/-) clear cell renal carcinoma cell proliferation: A possible mechanism coupling VHL tumor suppressor inactivation and tumorigenesis*. Proc Natl Acad Sci USA 2001, 98(4): 1387-92.

73. Xu, L., Tong, R., Cochran, D.M., Jain, R.K. *Blocking platelet-derived growth factor-D/platelet-derived growth factor receptor beta signaling inhibits human renal cell carcinoma progression in an orthotopic mouse model*. Cancer Res 2005, 65(13): 5711-9.

74. Na, X., Wu, G., Ryan, C.K., Schoen, S.R., di'Santagnese, P.A., Messing, E.M. *Overproduction of vascular endothelial growth factor related to von Hippel-Lindau tumor suppressor gene mutations and hypoxia-inducible factor-1 alpha expression in renal cell carcinomas*. J Urol 2003, 170(2, Pt. 1): 588-92.

75. Rini, B.I., Small, E.J. *Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma*. J Clin Oncol 2005, 23(5): 1028-43.

76. D'Amato, R.J., Loughnan, M.S., Flynn, E., Folkman, J. *Thalidomide is an inhibitor of angiogenesis*. Proc Natl Acad Sci USA 1994, 91(9): 4082-5.

77. Gelati, M., Corsini, E., Frigerio, S. et al. *Effects of thalidomide on parameters involved in angiogenesis: An in vitro study.* J Neurooncol 2003, 64(3): 193-201.

78. Moreira, A.L., Friedlander, D.R., Shif, B., Kaplan, G., Zagzag, D. *Thalidomide and a thalidomide analogue inhibit endothelial cell proliferation in vitro*. J Neurooncol 1999, 43(2): 109-14.

79. Li, X., Liu, X., Wang, J. et al. *Thalidomide down-regulates the expression of VEGF and bFGF in cisplatin-resistant human lung carcinoma cells*. Anticancer Res 2003, 23(3B): 2481-7.

80. Klausner, J.D., Freedman, V.H., Kaplan, G. *Thalidomide as an anti-TNF-alpha inhibitor: Implications for clinical use.* Clin Immunol Immunopathol 1996, 81(3): 219-23.

81. Moreira, A.L., Sampaio, E.P., Zmuidzinas, A., Frindt, P., Smith, K.A., Kaplan, G. *Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation*. J Exp Med 1993, 177(6): 1675-80.

82. Sampaio, E.P., Sarno, E.N., Galilly, R., Cohn, Z.A., Kaplan, G. *Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes.* J Exp Med 1991, 173(3): 699-703.

83. Deng, L., Ding, W., Granstein, R.D. *Thalidomide inhibits tumor necrosis factor-alpha production and antigen presentation by Langerhans cells.* J Invest Dermatol 2003, 121(5): 1060-5.

84. Lu, K.Q., Brenneman, S., Burns, R. Jr., Vink, A., Gaines, E., Haake, A., Gaspari, A. *Thalidomide inhibits UVB-induced mouse keratinocyte apoptosis by both TNF-alpha-dependent and TNF-alpha-independent pathways.* Photodermatol Photoimmunol Photomed 2003, 19(6): 272-80.

85. Yata, K., Otsuki, T., Kurebayashi, J. et al. *Expression of angiogenic factors including VEGFs and the effects of hypoxia and thalidomide on human myeloma cells*. Int J Oncol 2003, 22(1): 165-73.

86. Eisen, T., Boshoff, C., Mak, I. et al. *Continuous low dose thalidomide: A phase II study in advanced melanoma, renal cell, ovarian and breast cancer*. Br J Cancer 2000, 82(4): 812-7.

87. Escudier, B., Lassau, N., Couanet, D. et al. *Phase II trial of thalidomide in renal-cell carcinoma*. Ann Oncol 2002, 13(7): 1029-35.

88. Motzer, R.J., Berg, W., Ginsberg, M. et al. *Phase II trial of thalidomide for patients with advanced renal cell carcinoma*. J Clin Oncol 2002, 20(1): 302-6.

89. Stebbing, J., Benson, C., Eisen, T. et al. *The treatment of advanced renal cell cancer with high-dose oral thalidomide*. Br J Cancer 2001, 85(7): 953-8.

90. Srinivas, S., Guardino, A.E. *Randomized trial of high and low dose thalidomide in metastatic renal cell carcinoma.* Proc Am Soc Clin Oncol (ASCO) 2002, 21: Abst 2403.

91. Daliani, D.D., Papandreou, C.N., Thall, P.F. et al. *A pilot study of thalidomide in patients with progressive metastatic renal cell carcinoma*. Cancer 2002, 95(4): 758-65.

92. Novik, Y., Dutcher, J.P., Larkin, M., Wiernik, P.H. *Phase II study of thalidomide (T) in advanced refractory metastatic renal cell cancer (MRCC): A single institution experience*. Proc Am Soc Clin Oncol (ASCO) 2001, 20: Abst 1057.

93. Hernberg, M., Virkkunen, P., Bono, P., Ahtinen, H., Maenpaa, H., Joensuu, H. *Interferon alfa-2b three times daily and thalidomide in the treatment of metastatic renal cell carcinom*a. J Clin Oncol 2003, 21(20): 3770-6.

94. Clark, P.E., Hall, M.C., Miller, A. et al. *Phase II trial of combination interferon-alpha and thalidomide as first-line therapy in metastatic renal cell carcinoma*. Urology 2004, 63(6): 1061-5.

95. Sella, A., Sternberg, C., Yarom, N. et al. *Phase II study of low dose thalidomide and interferon-alfa in metastatic renal cell carcinoma (RCC).* Proc Am Soc Clin Oncol (ASCO) 2003, 22: Abst 1614.

96. Nathan, P.D., Walker, D., Bridle, H. et al. *A phase II study investigating the use of thalidomide in conjunction with interferon-a in patients with metastatic renal cell carcinoma*. Proc Am Soc Clin Oncol (ASCO) 2001, 20: Abst 1058.

97. Nathan, P.D., Gore, M.E., Eisen, T.G. *Unexpected toxicity of combination thalidomide and interferon alpha-2a treatment in metastatic renal cell carcinoma*. J Clin Oncol 2002, 20(5): 1429-30.

98. Gordon, M.S., Manola, J., Fairclough, D. et al. *Low dose interferon-a2b (INF) + thalidomide (T) in patients (pts) with previously untreated renal cell cancer (RCC). Improvement in progression-free survival (PFS) but not quality of life (QoL) or overall survival (OS). A phase III study of the Eastern Cooperative Oncology Group (E2898).* Proc Am Soc Clin Oncol (ASCO) 2004, 23: Abst 4516.

99. Olencki, T., Malhi, S., Mekhail, T., Dreicer, R., Elson, P., Wood, L., Bukowski, R.M. *Phase I trial of thalidomide and interleukin-2 in patients with metastatic renal cell carcinoma.* Invest New Drugs 2006, 24(4): 321-6.

100. Schrader, A.J., Heidenreich, A., Hegele, A., Olbert, P., Varga, Z., Hofmann, R. *Second-line thalidomide/IL-2 therapy in metastatic kidney cancer - Results of a pilot study.* Aktuelle Urol 2006, 37(6): 429-35.

101. Schrader, A.J., Heidenreich, A., Hegele, A. et al. *Application of thalidomide/interleukin-2 in immunochemotherapy-refractory metastatic renal cell carcinoma.* Anticancer Drugs 2005, 16(5): 581-5.

102. Amato, R.J., Morgan, M., Rawat, A. *Phase I/II study of thalidomide in combination with interleukin-2 in patients with metastatic renal cell carcinoma*. Cancer 2006, 106(7): 1498-506.

103. Desai, A.A., Vogelzang, N.J., Rini, B.I., Ansari, R., Krauss, S., Stadler, W.M. *A high rate of venous thromboembolism in a multi-institutional phase II trial of weekly intravenous gemcitabine with continuous infusion fluorouracil and daily thalidomide in patients with metastatic renal cell carcinoma.* Cancer 2002, 95(8): 1629-36.

104. Choueiri, T.K., Dreicer, R., Rini, B.I. et al. *Phase II study of lenalidomide in patients with metastatic renal cell carcinoma*. Cancer 2006, 107(11): 2609-16.

105. Gingras, D., Boivin, D., Deckers, C., Gendron, S., Barthomeuf, C., Beliveau, R. *Neovastat — A novel antiangiogenic drug for cancer therapy.* Anticancer Drugs 2003, 14(2): 91-6.

106. Boivin, D., Gendron, S., Beaulieu, E., Gingras, D., Beliveau, R. *The antiangiogenic agent Neovastat (AE-941) induces endothelial cell apoptosis.* Mol Cancer Ther 2002, 1(10): 795-802.

107. Gingras, D., Renaud, A., Mousseau, N., Beaulieu, E., Kachra, Z., Beliveau, R. *Matrix proteinase inhibition by AE-941, a multifunctional antiangiogenic compound.* Anticancer Res 2001, 21(1A): 145-55.

108. Beliveau, R., Gingras, D., Kruger, E.A. et al. *The antiangiogenic agent neovastat (AE-941) inhibits vascular endothelial growth factor-mediated biological effects*. Clin Cancer Res 2002, 8(4): 1242-50.

109. Batist, G., Patenaude, F., Champagne, P. et al. *Neovastat (AE-941) in refractory renal cell carcinoma patients: Report of a phase II trial with two dose levels*. Ann Oncol 2002, 13(8): 1259-63.

110. Escudier, B., Venner, P., Stern, L., Donovan, M., Croteau, D., Champagne, P., Bukowski, R. *Prognostic factor in metastatic renal cell carcinoma after failure of immunotherapy: Lessons from a large phase III trial.* Proc Am Soc Clin Oncol (ASCO) 2004, 23: Abst 4547.

111. Presta, L.G., Chen, H., O'Connor, S.J. et al. *Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders*. Cancer Res 1997, 57(20): 4593-9.

112. Gordon, M.S., Margolin, K., Talpaz, M. et al. *Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer*. J Clin Oncol 2001, 19(3): 843-50.

113. Margolin, K., Gordon, M.S., Holmgren, E. et al. *Phase Ib trial of intravenous recombinant humanized monoclonal antibody to vascular endothelial growth factor in combination with chemotherapy in patients with advanced cancer: Pharmacologic and long-term safety data*. J Clin Oncol 2001, 19(3): 851-6.

114. Yang, J.C., Haworth, L., Sherry, R.M. et al. *A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer*. N Engl J Med 2003, 349(5): 427-34.

115. Elaraj, D.M., White, D.E., Steinberg, S.M., Haworth, L., Rosenberg, S.A., Yang, J.C. *A pilot study of antiangiogenic therapy with bevacizumab and thalidomide in patients with metastatic renal cell carcinoma.* Immunotherapy 2004, 27(4): 259-64.

116. Rini, B.I., Halabi, S., Taylor, J., Small, E.J., Schilsky, R.L., Cancer and Leukemia Group B. *Cancer and Leukemia Group B 90206: A randomized phase III trial of interferon-alpha or interferon-alpha plus anti-vascular endothelial growth factor antibody (bevacizumab) in metastatic renal cell carcinoma*. Clin Cancer Res 2004, 10(8): 2584-6.

117. http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=10227 (accessed 12/25/2006).

118. Hainsworth, J., Spigel, D., Greco, A. *Combination therapy with bevacizumab and erlotinib for patients with metastatic clear cell renal carcinoma*. Proc 23rd Annu Chemother Found Symp (New York) 2005, Abst 22.

119. Holash, J., Davis, S., Papadopoulos, N. et al. *VEGF-Trap: A VEGF blocker with potent antitumor effects*. Proc Natl Acad Sci USA 2002, 99(17): 11393-8.

120. Dupont, J., Schwartz, L., Koutcher, J. et al. *Phase I and pharmacokinetic study of VEGF Trap administered subcutaneously (sc) to patients (pts) with advanced solid malignancies*. Proc Am Soc Clin Oncol (ASCO) 2004, 23: Abst 3009.

121. Mendel, D.B., Laird, A.D., Xin, X. et al. *In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: Determination of a pharmacokinetic/pharmacodynamic relationship*. Clin Cancer Res 2003, 9(1): 327-37.

122. Raymond, E., Faivre, S., Vera, C. et al. *Final results of a phase I and pharmacokinetic study of SU11248, a novel multitarget tyrosine kinase inhibitor, in patients with advanced cancers*. Proc Am Soc Clin Oncol (ASCO) 2003, 22: Abst 769.

123. Rosen, L., Mulay, M., Long, J. et al. *Phase I trial of SU011248, a novel tyrosine kinase inhibitor in advanced solid tumors*. Proc Am Soc Clin Oncol (ASCO) 2003, 22: Abst 765.

124. Motzer, R.J., Michaelson, M.D., Redman, B.G. et al. *Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma.* J Clin Oncol 2006, 24(1): 16-24.

125. Motzer, R.J., Rini, B.I., Bukowski, R.M. et al. *Sunitinib in patients with metastatic renal cell carcinoma.* JAMA – J Am Med Assoc 2006, 295(21): 2516-24.

126. De Mulder, P.H., Roigas, J., Gillessen, S. et al. *A phase II study of sunitinib administered in a continuous daily regimen in patients with cytokine-refractory metastatic renal cell carcinoma (mRCC).* J Clin Oncol 2006, 24(18, Suppl.): Abst 4529.

127. Motzer, R.J., Hutson, T.E., Tomczak, P. et al. *Sunitinib versus interferon alfa in metastatic renal-cell carcinoma.* N Engl J Med 2007, 356(2): 115-24.

128. Escudier, B., Eisen, T., Stadler, W.M. et al. *Sorafenib in advanced clear-cell renal-cell carcinoma.* N Engl J Med 2007, 356: 125-34.

129. Hudes, G., Carducci, M., Tomczak, P. et al. *A phase III, randomized, 3-arm study of temsirolimus (TEMSR) or interferon-alpha (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor-risk patients with advanced renal cell carcinoma (adv RCC).* J Clin Oncol 2006, 24(18, Suppl.): Abst LBA4.